Dermatological preparations for the tropics. A formulary of dermatological preparations and background information on choices, production and dispensing.

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Dermatological Preparations for the Tropics,
A formulary of dermatological preparations and background information on therapeutic choices, production and dispensing
2nd revised edition

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To the reader of this book

Medicine and pharmacy are fast changing scientific fields. We have taken great care to ensure that perspectives, opinions and practical information in this book are up to date. We have also taken great care to provide correct information. However, the authors and publisher cannot be held responsible for any error in this book nor for the consequences of such errors.
We would appreciate to receive any ideas, comments and additions.

Books and separate CDs can be ordered from the publisher. This book and its supplements are also available in digital format via www.rug.nl/wewi/dermatology or directly at http://irs.ub.rug.nl/dbi/4fed64994b40a

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Preface

Skin diseases may often be forgotten by policy makers, but not by patients. Many adults and children suffer from common disorders such as pyoderma, scabies, acne, dermatophytosis, skin warts and pediculosis capitis leading to much discomfort, medical expenses and loss of schooldays.

In industrialized countries effective and convenient treatments are easily available, and are usually reimbursed by health insurance. In low- and middle income countries (LMICs) and especially for the poorer segments of the population, the situation is different. Many patients first try their luck with the local store or the traditional healer, and only visit a clinic or hospital when the disease has progressed to an advanced stage. And when the diagnosis is finally made the patient, or the parent, often receives a written prescription to buy the treatment in a private pharmacy.

In LMICs up to three quarters of medical expenses are paid out of pocket. Poor households in LMICs spent up to 9.5% of their household expenditure on medicines, compared to 3.5% by the poor in high-income countries. Surveys from over fifty LMICs have shown that, on average, more than half of essential medicines are out of stock in public sector facilities, forcing patients to the private sector where brand preferences lead to prices which are 3-5 times higher than those of simple generic products. This picture is especially relevant for dermatological diseases, for which many facilities cannot afford to supply all patients with ready-made dermatological ointments and creams.

This book is the very welcome second revised edition of a publication that has stood the test of time. It brings the cost-effective treatment of common skin diseases within reach of all general physicians, clinical officers and nurses in rural clinics and district hospitals. The book also offers very practical guidance to pharmacists and pharmacy technicians in larger hospitals to prepare simple dermatological formulations at very low cost.

From an industrial development point of view, domestic production of skin preparations is a good start for building self-reliance in medicine manufacturing. Small-scale production of skin preparations does not require much capital investment, and the products can be adapted to local preferences and labeling. This business case is much easier to make than for manufacture of tablets and injections which require much more capital investment and technical sophistication, and which face immense global competition from large-scale production from countries like India and China.

The approach of this book is also very much in line with WHO's concept of essential medicines: a limited range of carefully selected essential medicines leads to better treatment and lower costs. The book is especially recommended for use by publicly funded or faith-based not-for-profit health care services – in other words, in situations where the health care provider wants to make an honest effort to supply the patients with cheap and cost-effective treatment.

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Former Director of Essential Medicines and Pharmaceutical Policies, WHO, Geneva

Preface to the 2nd edition

This formulary is a publication of the Science Shop (*Wetenschapswinkel*) at the University of Groningen in the Netherlands. The local production of medicines in tropical developing countries and regions is one of its fields of interest.

Skin diseases are common reasons for seeking medical advice all over the world, and even more so in developing countries (1,2). Up to 20% of people asking for treatment in primary care do so because of skin diseases. Although skin diseases are generally not life threatening, they may cause much discomfort and often have serious social implications. For example, scabies is a common skin disease. At any given time the worldwide burden of disease is about 300 million people (3). Most of these people live in developing regions and countries around the world. The highly negative influence of the disease on their quality-of-life forces even very poor patients to spend their money in search for an effective treatment they will most likely not find (4).

During the three years (1977-1980) that one of the authors of this book, Vincent Gooskens, worked as a dermatologist for the Malaŵian government, he experienced the differences between working in a skin clinic in a developed Western country and in a tropical developing country. Nearly all common skin diseases that are present in the Netherlands were just as common in Malaŵi, but a number of skin diseases, including scabies, pyoderma and fungal skin infections, were far more prevalent in Malaŵi. Together with his Malaŵian counterpart, L. Chalira, Gooskens experienced that 90% of their outpatients were effectively treated with cheap and simple medication.

The vast majority of patients with a common skin disease in Sub-Saharan African countries, such as Malaŵi, who ask for medical advise, will never see a doctor. Most likely they are treated by a traditional healer or a health worker with little training, in a primary health centre or an outpatient department of a hospital. The health worker can be a medical assistant, nurse or clinical officer, with access to almost none, or very few medications. In order to improve the care of patients with common skin diseases, it is necessary to train the health workers who will actually see and treat these patients, and to provide them with effective medications that are as cheap as possible in order to be affordable. In Malaŵi a simple booklet with essential knowledge about common skin diseases and their treatment with cheap and effective medications was used (5) and the Ministry of Health in Malaŵi decided to have these medications produced locally and distributed all over the country. Gooskens left Malaŵi and his Malaŵian counterpart, an inspired teacher who continued to train medical assistants and clinical officers for many years. Despite his efforts, Chalira could not prevent the production and distribution of skin medications to gradually decline again. Although their efforts did

not last, comparable constructive efforts were described more recently by Mahé in Mali (2) and is hopefully followed by many more. A useful pocketbook on the diagnosis and treatment of common skin diseases in Africa has become available free of cost from TALC UK (6).

The choice of medication should always be based on scientific grounds. Throughout the years little scientific work has been done to compare the effectiveness of cheap medications, that are produced locally, with the vast and ever growing number of more expensive medications produced by pharmaceutical industries. In this book we collected the available scientific data to make an optimal choice of effective and cheap medications for common skin diseases that can be produced locally and made available in primary health centres and hospitals in developing countries and regions. Since no new books on this subject have been published after the first edition in 1990, we decided to update the book for a second edition.
Although this book contains a lot of interesting information for all dermatologists and pharmacists, it is especially meant for those who want to improve the dermatological care in developing countries and regions. We hope that trainers, medical assistants, clinical officers, and trainees in general in those countries will use the book in the training centres for dermatology. The book tells everything you need to know about the choice of effective and cheap medications for common skin diseases and how to produce them locally.

We suggest that any training centre for dermatology in a developing country or region should co-operate with one or more pharmacists in a well-equipped pharmacy where effective and cheap medications are produced. Such a collaboration can stimulate the use of these medications within the dermatology training programmes. The people trained to use them may convince decision makers in their own Ministries of Health of the importance of local production of cheap and effective medications which are made available in health centres and hospitals across the country. They can also advocate the importance of giving a short practical training to all health workers in primary health care in order to teach them to recognise the most common skin diseases and the way to treat these diseases with the available cheap and effective medications. This strategy of improved dermatology training, in combination with the local production of medicines, could enormously improve the dermatological care in the whole country at a cost that is most certainly affordable. An example of such a development is the initiative of the International Foundation for Dermatology to donate a Compounding Facility for Dermatologic Topical Medications to the Regional Dermatology Training Centre (RDTC) in Moshi, Tanzania, and to organise the help of two pharmacists (7). In a recent initiative, further compounding equipment was donated to the RDTC and to the Haydar University in Mekelle, Ethiopia.

This book has been written to give hope to less privileged people with common skin diseases. Although it is far from easy to organise effective treatment for them, the low costs of the medications in this book provide an important condition for realisation.

October 2012, Groningen, the Netherlands

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Contents

PART 3: MONOGRAPHS

1 How to use the book

Dermatological preparations for the tropics brings together practical and background information for local production, dispensing and use of dermatologicals in the least developed countries and regions around the world. It is set up as a formulary, a collection of medicines that is chosen according to specified criteria. The list of dermatological medicines is based on a broad range of skin diseases that is highly prevalent in the least developed regions of the world. As differences can be significant, each country or region should develop its own dermatological formulary according to the local situation concerning medical needs, health care system, resources, and pharmaceutical production facilities.

The book aims to facilitate local choices by providing sufficient information to select and produce dermatologicals – what to prepare for which indication and how to do this – as well as to provide background information on choices and methods – why to do it this way. We hope the book may serve a wide range of users in a wide range of situations.

The book can be used in many ways. The information can be jointly used by doctors, pharmacists, nurses, medical officers, and other health care workers, together with government and non-governmental organisation (NGO) officials to develop local drug policies and formularies for dermatologicals. Consequently, the ones who treat the majority of patients with skin diseases can use the book to learn how to dispense the available medications and facilitate appropriate use.

In our selection of preparations, methods, and relevant information we focused on simple and effective, cheap and safe. If we stick to well known, time-honoured preparations, it is because they are still valued, relatively affordable and well documented. Well documented, but often only in older literature. In our opinion the absence of recent literature alone, is insufficient reason to disqualify an active ingredient or a preparation.

The book can also be used as a manual for the production and dispensing of dermatologicals in tropical countries. It contains a number of chapters with practical information on relevant topics.

As we believe it is not only important to know what to do and how to do it, but also to know why, the book includes a number of chapters with background information. As a result, it can also be used as a textbook for teaching and learning pharmacotherapy of skin diseases and pharmaceutical manufacturing. The background information is sometimes brief, but for other topics we considered it relevant to explain in-depth the reasons for our choices. These in-depth explanations in chapters 5 and 9 are indicated by printing the text in a lighter shade. The reader may consider skipping this detailed information.

Part I: Pharmacotherapy of skin diseases

The first part of the book is written from a medical and pharmacological point of view. Its contents may be particularly useful for the selection of active substances and pharmaceutical forms for the local formulary. It can also be used as an introduction in pharmacotherapy of skin diseases.

Chapter 2 introduces the essential drugs concept, basic and specific needs for dermatology in tropical conditions, and our criteria for selecting preparations for the formulary. In other words, it explains why developing a local dermatological formulary and local production facilities are of strategic value to communities in the least developed regions around the world.

Chapter 3 lists the indications and the dermatological preparations included in the formulary, together with information on how much to dispense to a patient. It provides a quick and practical overview. The reader may notice that rare skin diseases requiring specialised care are not included in the book. The reason for this choice is that local production for primary health care in regions where resources are scarce, can be best set up to serve the greatest denominator.

Chapter 4 deals with the treatment of skin diseases. The backgrounds of the therapeutic choices of the formulary and specific categories of drugs are discussed including: anti-infective drugs used in bacterial, mycotic and parasitic infections, burn wounds, the treatment of ulcers in leprosy, corticosteroids, astringents, keratoplastics and keratolytic agents, moisturisers with special attention to the management of dry skin in leprosy, antimitotics, antipruritic preparations, "indifferent" vehicles, and sunscreen agents.

Chapter 5 lists the dermatological vehicles and how suitable they are for therapy in tropical conditions. The vehicles included are: ointments, pastes, creams and shake solutions. Various formulations are discussed in relation to production and use in the tropical climate, and under resource scarce conditions.

Part II: Small scale local production

The second part of the book is written from a pharmaceutical point of view. It provides an overview of standards and methods for the local production of dermatologicals. This part of the book is not intended as blueprint for setting up local production, but is meant to provide a background for designing local production facilities according to specific local needs, resources and financial possibilities.

Chapters 6, 7 and 8 can be used for setting up local production facilities, and for the training of personnel. Chapter 6 describes the basic standards of Good Manufacturing Practice (GMP) for local production facilities in the least develop regions. It includes working with personnel, hygiene, premises, equipment, and manufacturing procedures.

Chapter 7 can be read as a practical guide to turn the GMP standards of chapter 6 into practice. It deals with general notes on quality assurance, production forms and administration, packaging, labelling, storage, weights and measures.

Chapter 8 focuses on basic pharmaceutical methods such as weighing, measurement of liquids, making up to volume or weight, sieving, mixing and heating.

Chapter 9 provides background information on the chemical, physical and microbial stability of dermatological preparations. Where relevant, stability issues are also discussed in relation to packaging. Of specific concern is the information on the chemical stability of relatively unstable therapeutics. Two tables summarise the relevant data on chemical and physical stability.

Chapter 10 provides a vocabulary of the pharmaceutical terms used in the formulary, and chapter 11 lists the synonyms of preparations and raw materials.

Part III: Monographs

Part three of this book contains the preparation and raw material monographs. Chapter 12 lists 41 monographs of the preparations included in this dermatological formulary. Thirty-five monographs contain the actual recipes (the formulation and preparation methods). For six preparations we do not recommend local production for practical or safety reasons. The monographs also provide relevant information on packaging, storage, and therapeutic use. To facilitate dispensing to the patients, the monographs contain information on dosage, instructions for use, precautions, general side effects and risks during pregnancy and breast feeding. Furthermore, the preparation monographs inform about dealing with intoxications. The monographs are set up for small scale production. The recipes are for amounts of 100 g or 100 ml. Stock preparations are usually prepared in quantities of 1 kg or 1 litre, or even larger batches. Master production forms for stock preparations of 1 kg or 1 litre are included on the cd that comes with this book. They can also be found on the internet via www.rug.nl/wewi/dermatology or directly at http://irs.ub.rug.nl/dbi/4fed64994b40a.

Chapter 13 lists all the raw materials that are used in the preparations. In addition to descriptions of the raw materials, the monographs provide information on their storage and how to avoid hazards while working with them.

Appendix: Water preparation

As safe water is an essential ingredient of most dermatological preparations, the book contains information on the procurement of water suitable for small scale production.

Index and literature

The book includes a general index with keywords, preparation names, and raw material names. Difficult words and technical terms are not avoided in the book. Technical terms that are used in the chapters with practical information, i.e., 3, 6, 7, 8, 12 and 13, are explained in chapter 10, the vocabulary. Difficult words in the chapters with medical and pharmaceutical backgrounds, i.e., 4, 5, and 9, are not explained explicitly. These chapters include literature references. As the preparations in the formulary and their preparation methods are based on the background chapters, the practical chapters do not include literature references. Thus, the general index and the list of synonyms are useful to find relevant sources of information.

Further reading

For further backgrounds on the basic information we recommend the book *Pharmaceutical compounding and dispensing* by Marriott and co-authors (1). More in-depth information and theoretical backgrounds are found in the book *Aulton's Pharmaceutics* (2). The *Pharmaceutical Codex* is a valuable reference for all aspects of pharmaceutical compounding and dispensing (3). Another valuable reference on active and other ingredients is *Martindale's Extra Pharmacopoeia* (4). Since the preparations in the dermatological formulary often contain ingredients that have been in use for longer times, older editions of the Martindale may suffice. Finally, the web-site "e-drug compounding (www.openapo.info)" gives more preparation formulae and other useful information (5).

As a useful and practical introduction to skin diseases in Africa, we recommend the book *Common skin diseases in Africa, an illustrated guide* by Van Hees and Naafs, which is freely available from TALC UK (6). The *ABC of Dermatology* by Buxton provides more detailed information on skin diseases and their management (7).

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2 Dermatological preparations for the tropics

2.1 Context of the project

Since the foundation of the Science Shop for Medicines (*Wetenschapswinkel voor Geneesmiddelen*) in 1979, which has now become a science shop covering a broader area of the natural sciences, a host of questions have been asked by health workers in developing regions and countries. Many of these questions are concerned with storage and local preparation of pharmaceuticals. Conducting research to find relevant answers has remained important over the years.

The incidence of dermatological disorders in (tropical) developing countries or regions is very high. The incidence of non-infectious skin disorders is considered more or less constant throughout the world, although there are some regional variations (1,2). In contrast, the incidence of infectious skin diseases is much higher in developing than in developed countries (3). Scabies, mycotic infections and pyoderma are among the most common skin diseases in these countries, resulting in an estimated overall incidence of dermatological disorders, which is twice as high as that of modern Europe.

Socioeconomic factors are the most important factors determining the incidence of infectious skin diseases. Relevant factors include housing and sanitary conditions, water supply, preventive health care, education, nutrition and the availability of curative medicine. The patterns and incidence of infectious diseases in today's developing regions and countries are comparable to the situation in Europe at the end of the 19th century. Changes in Europe came from better housing, piped water supply, sewerage, higher wages, educational programs and political will. In comparison, the use of improved curative medicine played only a minor role. This is illustrated by the fact that most of the rapid improvements in the situation in Europe were seen before anti-infective treatment (antibiotics) became available (1,4). It is likely that similar patterns will be observed in tropical developing countries and regions.

The primary health care (PHC) concept was developed by the World Health Organization (WHO) as one of the main instruments for reaching the ambitious goal of "health for all" in the foreseeable future. Skin diseases are one of the main reasons for seeking medical advice in developing countries where PHC is offered (3). Up to 20% of people asking for treatment in primary health care do so because of a skin disease. Nevertheless, until now, little attention has been paid to the provision of adequate dermatological drugs for use in primary health centres and hospitals in these countries. In 1990, focusing on local production, we decided to publish a formulary that could help meet the basic dermatological needs of the majority of the population in tropical developing regions and countries. Remarkably, very little new information has been published on the subject since then. Sadly, pharmacological and pharmaceutical research is generally driven by market opportunities, less by how valuable treatments are to patients, medical staff, communities and society as a whole.

2.2 Essential drugs and formularies

The first WHO Essential Drugs List was published in 1977 (5). The purpose of this list was to extend the availability of drugs to the populations whose needs could not be met by the existing system, by limiting the number of drugs to only those that were considered essential. The most important selection criteria were effectiveness, safety, and the necessity for treatment of the main health problems. Drugs that were selected according to these criteria should be made available to all people. Limited lists, which are often called formularies, can also be useful for promoting rational prescribing (e.g., hospital formularies in the Netherlands).

As the differences between countries or even regions can be significant, the preparation of one uniform drugs list is not possible. Each country or region should, therefore, develop its own list depending on local needs, health care system, financial resources, as well as other genetic, demographic and environmental factors (see figure 2.1). Furthermore, there is a need to regularly review essential drugs lists as situations may change in time and more information and new drugs may become available. The latest review of the WHO Essential Drugs List is the 17th edition of March 2011 (6).

To make sure that choices are as objective as possible, they should be based on well formulated criteria. The WHO indicates some of the criteria to be used. For example, choices should be based on a benefit/risk ratio as determined in controlled trials. Generic names should be used whenever feasible. Choices between therapeutically equivalent drugs should be based on benefit/cost ratios, stability, the amount of information available, kinetic parameters and the possibility for local production of the drug. Quality must be guaranteed and the local situation should be carefully considered.

Figure 2.1. Interior of a pharmacy

Since 1979, the WHO has specified pharmaceutical forms in the Essential Drugs Lists (7). This is important because a drug consists of both an active ingredient and a vehicle. The route of administration and the vehicle used are both main factors that determine price, effectiveness, stability and pharmacokinetics. If the essential drugs concept is ever to be effective, not only should the number of active ingredients be limited, but the number of preparations as well. There are only a few cases requiring more than one form or vehicle, for example when a drug (the active ingredient) is used for diseases requiring different pharmaceutical forms. In instances when different forms are considered therapeutically equivalent, the WHO may only vaguely indicate the pharmaceutical form. The cheapest available preparation should then be chosen.

Primary health care depends on local health workers. They are considered an essential link to getting health services as close to the people as possible, along with facilitating participation. Usually, these local health workers have little formal training. In many villages facilities are generally quite basic. Consequently, it is recommended to select a limited list of essential drugs suitable for use at village or regional level. Such a selection, or putting together a formulary, can only be done at a national or regional level as it is impossible to prepare such a list internationally (3,5,8).

For example, a primary health care setting with very limited financial resources may restrict the number of preparations to six. Such a limited formulary could contain calamine lotion as a soothing and antipruritic preparation, a scabicide, povidone iodine solution as anti-infective drug, an emollient such as emulsifying ointment, and a preparation against chronic itching skin diseases, such as hydrocortisone ointment. More preparations can be suitable for the secondary health care level, according to local needs and production facilities.

2.3 Local production of drugs

Local production may be important for increasing the independence of developing countries/regions and enhancing self-reliance, participation, knowledge and experience (4,9-13). The majority of common skin diseases can be treated with cheap and effective medication. Recently, the WHO has revived its interest in the local production of medicines, vaccines and other medical products (12). Local production may be cheaper and can be implemented stepwise, starting with packaging and simple preparations (see figure 2.2). Some developing countries, like India and Brazil have developed extensive national drugs industries (13). Local production may help increase access to essential medicines, but this is by no means guaranteed and a considerable discussion on this topic is still ongoing (13). Considering factors like the local situation, human and financial resources governments must decide whether, and to what extent, local production is feasible. Other factors include cost effectiveness, stability, dependence on industrialised countries, and the quality of local infrastructure. More detailed and updated information is available on the WHO website (14).

A comprehensive analysis of the costs and profits of local production of drugs is difficult. Both costs and profits may be financial and non-financial, short-term and long-term. Starting local production often means investing (a lot of) money, most probably hard foreign currency. On the positive side, highly qualified work remains or can be developed in the country, and the purchase of drugs can start to put less pressure on foreign currency reserves. In the long run, independence may grow. In some cases, particularly the production of intravenous fluids and other solutions, local production can easily become cost-effective as transport costs are a major part of the price of such drugs, and these preparations mainly involve locally available raw materials, such as water (15). Setting up an infusion production unit in Tanzania turned out to be a good example of this principle (16).

As a general rule, unstable drugs should be kept away from contact with water, because this fastens their decay. As a consequence, the stability and shelf life of preparations that contain water, and most dermatological drugs do, is limited. Thus, the advantages of preparing these drugs at or near the places where they are needed are clear. For example, the quantities for production can be easily adjusted to local needs taking into account shelf life, which in turn will reduce waste.

Dependence on industrialised countries may persist even when drugs are locally produced (13). Such situations may exist when production facilities are still owned by foreign, often transnational companies or their local subsidiaries, or when most raw materials need to be imported, particularly during the first stages of local production. In the latter case, dependence is only shifted from finished products to raw materials. Cooperation between developing countries is important to (partly) offset such dependences, for example, by exchanging knowledge and the few raw materials that are regionally produced. Clearly, dependence will not disappear overnight, but the issue can be tackled. Governments and other stakeholders need to address these problems. If no action is taken towards the development of local production, it will most certainly not happen.

Even ideal drugs are effective and safe only when they are prescribed and used correctly. Good information is crucial. Information should be given in local languages, accompanied with pictograms. Both written and visual information should take full account of the local situation and customs and should, therefore, be locally created. Additionally, information is best provided on the packaging, more specifically, the primary packaging as it remains close to the product. Thus, several strong arguments favour local packaging.

Figure 2.2. Setting up a dermatological formulary and production facility as collaborative processes

Quality assurance is also crucial for both locally produced and imported drugs. National or regional quality control laboratories may play an important role in accomplishing this task. Good quality assurance may increase the acceptance of locally produced drugs by the communities that need them. Quality assurance depends on preparation methods and the organisation of quality assessment. It is important to take this aspect into account when considering the selection of preparations and preparation methods (8).

2.4 Conclusions

Skin diseases are far more common in developing regions and countries compared to developed countries, due to a higher incidence of infectious skin diseases caused primarily by an array of socioeconomic factors. Infectious skin diseases may cause a lot of discomfort and impact the quality of life to a degree that people desperately want to get rid of them. The treatment may also cause a serious financial burden for an individual family or a community (17). To secure long-term improvements, relevant socioeconomic factors need to be adequately addressed. Fortunately, in the meantime, it is possible to treat infectious skin diseases with effective and cheap medication. Local production of cheap and effective medication forms the economic solution to treat the majority of patients with skin diseases in poor regions of the world. Such drugs for treatment of common skin diseases should hence be a part of an integrated approach to health care in developing countries and regions. They are also the main subject of this book.

Local production may play an important role, especially in the long run, in reducing cost and dependence on other countries, enhancing self-reliance and reaching as many people as possible. To make the best use of limited resources and ban useless, dangerous and overpriced drugs, implementation of the essential drugs concept is crucial.

Primary health care is the best way to reach the majority of a population. Therefore, in this book we focus on compiling a limited list of effective dermatologicals that can be safely prescribed by village health workers as well as prepared in the country or region itself. In addition, we will consider drugs for use in hospitals. The limited list, or formulary, may need local adaptation, which is most likely the result of deletion of certain drugs, rather than the addition of other ones.

2.5 Selection criteria for the formulary of dermatological preparations

The principles set out in this chapter are translated into the following selection criteria.

* ***Need***

The preparation must be effective for the treatment of skin diseases that affect many people. There is no need for drug treatment if it is not effective, or when non-drug treatment is as good as, or better than the drug.

* ***Benefit/risk ratio***

The effectiveness of a drug must be well documented, preferably with controlled clinical trials. In the case of equal effectiveness, the drug that has the fewest side effects should be selected. If misuse or abuse of a drug can result in major risks, the use of that drug should be avoided. Information, such as tropical climate factors, referring to the specific context in developing countries or regions, should be considered when weighing the

risk/benefit ratio, instead of looking only at relevant scenarios in Western countries. Specific conditions of the population that will be using the drugs, i.e., the presence of malnourishment or endemic diseases, such as hepatitis, malaria or AIDS need to be taken into account in the risk/benefit assessment of drugs.

* ***Benefit/cost ratio***

Benefits and costs should be carefully evaluated. Cost estimates need to be based on treatment prices and not unit prices. Transport costs should also be considered. Estimates of treatment cost should include any additional costs, such as bandages used or hospital admissions. Also, non-financial costs and benefits should be taken into account, for example, the need for extra hospital visits.

* ***Vehicle***

Selection of drugs is incomplete if only active ingredients are considered. This holds true for any drug, but especially so for dermatologicals. These preparations should be washable, non-occlusive and suitable for the given skin conditions. They should be easy to pack and simple to apply, even under tropical conditions.

* ***Stability***

Raw materials and preparations must show good chemical, physical and microbiological stability under adverse storage conditions. When excessive chemical degradation of an ingredient or toxicity of degradation product(s) is expected, the drug or ingredient should be avoided.

* ***Preparation***

The formula must be easy to prepare by personnel with relatively little training. Preparation must be feasible with only a limited number of simple utensils. Preparation methods should guarantee the highest possible quality.

* ***Raw materials***

Raw materials must be cheap and easy to obtain from local or regional sources. They must also be simple to process. Any hazardous materials (e.g., toxic, inflammable or explosive) should be avoided.

* ***Packaging***

A general requirement is that packaging should ensure integrity of the preparation and protection against adverse external effects. The packaging of drugs meant for use in tropical countries should also be light, reusable, providing adequate protection for the preparation against evaporation, adsorption of water, and excessive exposure to light.

Likely, no drug will meet all these standards. The best drugs should be chosen considering the local situation. This should preferably be done on a national or regional basis, but it is also possible to indicate some generally applicable drugs and prepare a basic formulary for use in tropical countries. Still, these formularies should be reconsidered by the local health authorities and experts who have sufficient knowledge about skin diseases that need to be treated, circumstances of production, condition and use of health care facilities. In certain cases more than one suitable preparation is identified. In these cases the choice should be based on the local situation.

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3 Indications for the preparations and how much to use

3.1 Introduction

This chapter contains a list of skin diseases which can be treated with the preparations in this formulary. Included are the most common skin diseases, not the rare diseases requiring specialised treatment. The preparations are listed in their preferred order of choice. The reasoning for this order is briefly explained in the preparation monographs in chapter 12.

Some preparations are unsuitable for primary health care. They need more specialised expertise or special precautions for safe prescription, dispensing, and use. Therefore, the term "2nd line" is added to these preparations. Detailed information on the backgrounds of the preparation choices, their therapeutic effects, and pharmaceutical considerations, is found in chapters 4, 5 and 9 of this book.

General guidelines for the amounts of dermatological preparations to be prescribed, dispensed, and used, are also given in this chapter.

3.2 List of indications and preparations

Acne
- salicylic acid solution 5%
- sulphur lotion 3%

Bullous dermatoses
- strong corticosteroid preparation + indifferent vehicle *
- potassium permanganate solution

Burns
- silver sulfadiazine cream
- silver nitrate solution 0.5%

Corns and calluses
- salicylic acid strong ointment 30%

Dermatitis/eczema
- hydrocortisone cream or ointment 1%
- tar cream, solution or paste

– strong corticosteroid preparation + indifferent vehicle *
– calamine lotion
– zinc oil

Disinfection: e.g., tools for surgery
– industrial methylated spirit 70%

Disinfection: intact skin
– povidone iodine solution
– chlorhexidine solution 1%
– iodine tincture or solution 2%

Disinfection: wounds
– chlorhexidine solution 0.1%
– povidone iodine solution 10%
– iodine solution or tincture 2%

Dry skin
– indifferent vehicle *
– urea cream or ointment 10% (2nd line)

Fungal infections: tinea corporis, tinea pedis
– Whitfield's cream or ointment 5%-5%
– miconazole cream 2%

Fungal infections: Candidosis
– miconazole cream 2%
– gentian violet solution 0.5%
– nystatin preparation

Ichthyosis
– indifferent vehicle *
– urea cream or ointment 10%

Immunological skin disorders
– hydrocortisone cream or ointment 1%
– strong corticosteroid preparation + indifferent vehicle *

Leprosy (dry skin due to)
– indifferent vehicle *

Leg ulcers: e.g., in leprosy
– potassium permanganate solution
– zinc paste 50%

Parasitic infections: scabies/pediculosis
- benzyl benzoate emulsion 25%
- lindane cream 1%
- sulphur cream or ointment 10%

Photodermatoses
- sunscreen FAA
- zinc paste 50%

Pigmentary disorders: vitiligo
- strong corticosteroid preparation + indifferent vehicle *

Pityriasis versicolor
- sodium thiosulphate solution 10%

Protection
- zinc paste 50%
- petrolatum

Pruritus
- calamine lotion
- hydrocortisone cream or ointment 1%

Psoriasis
- strong corticosteroid preparation + indifferent vehicle
- salicylic acid ointment 5%
- tar cream, solution or paste (2nd line)
- dithranol paste or cream (2nd line)

Pyoderma
- povidone iodine solution 10%
- potassium permanganate solution
- gentian violet solution 0.5%
- chlorhexidine solution 1%

Sunscreen agents
- sunscreen FAA
- zinc paste 50%

Viral diseases: common warts
- salicylic acid strong ointment 30%

* Indifferent vehicle: we recommend using emulsifying ointment to keep the skin healthy and in good condition. Vegetable oils, basic cream or petrolatum are good alternatives.

2nd line: for the safe prescription, dispensing, and use of these dermatological preparations specialised expertise is required. Such care is generally not available in primary health care settings in developing countries or regions.

3.3 How much to use

It is often difficult to determine the quantity of a certain preparation that is required for the treatment of a patient. For a limited number of preparations the standard quantity for a complete cure per patient can be determined. This is for example the case for the treatment of scabies with benzyl benzoate lotion. Standard quantities for specific indications are mentioned in the preparation monographs (chapter 12) whenever possible.

To obtain a pharmacological effect, dermatological preparations are applied on the skin in a thin layer, usually 1 - 2 times daily. The 'fingertip unit' (FTU) is a practical aid for dosing dermatological preparations, especially for highly active preparations such as corticosteroids. An FTU is one dash of cream or ointment with the length of the distal bone of the forefinger of an adult. One FTU equals approximately 0.5 g cream or ointment and is sufficient to cover 300 cm^2 skin. Depending on the part of the body to be treated, one or more FTUs are used (see table 3.1). In addition, the concentration of the active drug ingredient in the vehicle determines the dosage.

Table 3.1. Fingertip unit (FTU) dosing for ointments and creams per application

	Head and neck	***Arm and hand***	***Leg and foot***	***Trunk (front)***	***Back and bottom***
Age	***Number of FTU per application***				
3 - 12 months	*1*	*1*	*1½*	*1*	*1½*
1 - 2 years	*1½*	*1½*	*2*	*2*	*3*
3 - 5 years	*1½*	*2*	*3*	*3*	*3½*
6 - 10 years	*2*	*2½*	*4½*	*3½*	*5*
Adult	*2½*	*4 **	*8 ***	*7*	*7*

* For only one hand of an adult 1 FTU is required
** For only one foot of an adult 2 FTUs are required

The quantity required for a particular patient can also be calculated with information on the dose and duration of the therapy, and the area of the skin that will be treated. For example, when a physical action is desired to hydrate the skin, dermatological preparations are amply applied, as often as necessary, but at least twice a day. Indifferent preparations, such as basic cream or emulsifying ointment, are often used for this purpose. Table 3.2 shows standard quantities to supply for use on specific parts of the body. Dermatological preparations should preferably be dispensed in a limited number of standard quantities. For semisolids 5g, 15g, 30g, 50g and 100g are suitable standards, and for liquid preparations 50 ml, 100 ml, 200 ml and 500 ml are suitable.

Table 3.2. Standard quantities required for adults to treat a particular part of the skin two times daily for one week. The quantities are rounded off to the nearest standard quantity.

Part of the body	*Cream / ointment / paste*	*Liquid preparation*
Face	*5 - 15 g*	*100 ml*
Hand	*15 - 50 g*	*200 ml*
Arm	*50 - 150 g*	*200 ml*
Leg	*100 - 300 g*	*200 ml*
Trunk	*200 - 500 g*	*500 ml*
Whole body	*500 - 1500 g*	*500 ml*

Creams are generally more economic than ointments or pastes because they are easier to apply. The amount of an ointment required for a specific treatment is 1.5 - 2 times as high as compared to the quantity of a cream for the same treatment. When a paste is used, 2 - 3 times as much is required as compared to a cream.

For certain preparations a maximum dose is indicated in the monograph. The quantity supplied to a patient should always be below this maximum dose.

Children have a smaller skin surface than adults, and dispensing smaller quantities is generally sufficient. The strength of preparations for children, the frequency of application and the duration of therapy in children are usually the same as for adults. However, certain dermatological preparations may be more dangerous to children. If so, the need for treatment and the optimal dose should be determined carefully, and special precautions may be required. Information on this subject is included in the preparation monographs whenever relevant.

4 Dermatological therapy

This chapter deals with therapy for skin diseases with a focus on tropical developing countries. It provides background information on the choices of the preparations and active ingredients included in the formulary. First a general introduction on the biopharmacy of dermatologicals is given, followed by a review of the most prevalent skin diseases, their recommended pharmacotherapeutic approaches, active ingredients and preparations.

4.1 Introduction

Skin diseases are generally not life-threatening, but may cause considerable discomfort and have serious social implications justifying (drug)treatment. The preferred treatment of dermatological disorders is topical application of an active drug substance. The therapeutic effect is the result of the pharmacological properties of the active drug, in combination with the nature of the vehicle. In addition to the desired local effect, the application of a drug substance on the skin may exert a systemic effect following (undesired) absorption.

4.1.1 Biopharmacy of dermatological preparations

The skin protects the body against harmful influences from the outside. Three skin layers are distinguished. From the outside to the inside these are: epidermis, dermis and subcutis. The outer layer of the epidermis is called the stratum corneum, which consists of dead, keratin containing cells. The pH of the healthy skin surface is approx. 5.5. The (intact) stratum corneum is considered a lipoid membrane forming a barrier against water, chemicals and micro-organisms. The stratum corneum can take up considerable amounts of water. Occlusion, which is the covering of a part of the skin after application of a dermatological preparation, or bathing, can raise the water content of the stratum corneum from 10-20% to 50-75%. The effect of hydrating the stratum corneum is that it becomes more permeable, also for drugs, and its barrier function is reduced.

Upon application of a dermatological preparation on the skin the active drug needs to penetrate into the skin to reach its site of action and exert an effect. The extent and speed of penetration depend on the partition equilibrium between the dermatological vehicle and the stratum corneum. Driving forces for drug penetration into the skin are passive diffusion and osmosis. In addition, the skin condition (e.g., hydration, damage), the localisation on the body (plantar, palmar surfaces, around the eyes, genitals, axillae etc.) and the method of application (massage, rubbing) impact the level of penetration. In general, a lipophilic drug penetrates faster into the skin than a hydrophilic drug, and a lipophilic drug penetrates faster into the skin from an aqueous vehicle than from a fatty vehicle. The penetration of an active drug ingredient into the skin can be enhanced by occlusion and/or by using penetration enhancers. Factors determining the penetration of a drug substance into the skin are summarised in table 4.1.

Table 4.1. Survey of factors determining the penetration of a drug substance into the skin

Physico-chemical properties of the active drug ingredient	*Solubility*
	Lipophilicity
	Concentration in the vehicle
Basic constituents of the vehicle	*Lipophilicity of the vehicle*
	Surfactants
	pH
Contact surface	
Condition of the skin	*Localisation on the body*
	Damage to the stratum corneum
	Hydration
	Type of skin
External	*Occlusion*
	Penetration enhancers
	Rubbing
	Massage

The local application of a drug on the skin offers the advantage that only the afflicted tissue is treated. Locally applied drugs must have a good bioavailability. Preferably they are dissolved in the vehicle. All substances with a molecular weight below 500 Dalton penetrate into the stratum corneum, with the exception of extremely hydrophilic substances. Some drugs are able to enter into the general circulation after application on the skin, and may exert undesired systemic effects. Typical examples are corticosteroids, local anaesthetics and salicylic acid. Especially the damaged or pathologically changed skin harbours a higher risk of inducing systemic effects, because the natural barrier function of the skin is reduced or even absent under these conditions. Application of drug preparations in skin folds, groins, axillae, etc. generally lead to higher uptake of the active drug due to the type of skin in these places. Occlusion enhances hydration, and as a result enhaces penetration of many drugs into the skin. The same effect is obtained by adding a penetration enhancer to a dermal preparation (e.g., urea 5-10%, salicylic 2-5%, propylene glycol 10-20%).

The choice of the vehicle depends on:
- The condition of the skin. The aim of treatment is to restore hydration of the skin to a normal level. A rule of thumb is 'wet on wet and fat on dry' meaning that liquid cutaneous forms are applied on wetting skin parts, and semi-solid forms with a high fat content can be used for (very) dry skin conditions.
- The location on the body. For hairy skin, such as the head, an easily washable vehicle should be used. In wet skin folds an occlusive vehicle should be avoided.
- The acceptability for the user. An extremely fatty vehicle during daytime is generally undesirable from a cosmetic point of view.
- The constituents of the vehicle must be chemically compatible with the drug substance.

The physical properties of the vehicle can be used as follows to optimise therapy:
- Cooling and/or drying due to the presence of water or another volatile solvent (e.g., ethanol).
- Drying and protecting by dispersed indifferent solid substances (e.g., zinc oxide, talcum, starch).
- Counteracting dehydration by using hydrophobic ingredients (paraffin, petrolatum, which is also known as petroleum jelly or soft paraffin, glycerin, vegetable oils).

(Patho)physiological factors also determine the effectiveness of dermal preparations:
- The penetration rate of an active drug is higher when applied on thin skin (e.g., behind the ear, on the eyelid or scrotum) than when applied on thick skin (e.g., palm of the hand, sole of the foot).
- The penetration rate of a drug into damaged skin is higher than into intact skin.
- The penetration rate of a drug into hydrated skin is higher than into dry skin.

4.2 Infectious skin diseases and their treatment

4.2.1 Introduction

Infectious skin diseases are a major problem in the least developed regions around the world (see chapter 2). Among these, scabies, pyoderma and mycoses occur most often. Therapy can be both systemic and local, the choice being dependent on the nature of the disease and the place on the body where it occurs.

Antiseptics are used on living materials, and disinfectants are used on non-living materials, such as instruments. Antiseptics should be well tolerated and non-toxic, as they are intended to reduce the number of micro-organisms on the treated tissues.

There is a gradual difference between antibiotics and antiseptics. Antibiotics are derived from biological sources, they are active in low concentrations, and have a specific mechanism of action against a limited range of micro-organisms. Micro-organisms may develop resistance, rendering the antibiotics ineffective. Antiseptics are rather simple chemicals with a specific mode of action. They have less sensitisation potential, are less prone to resistance development, have a broad spectrum of action, but are generally more toxic in comparison to antibiotics. Antiseptics are preferred for the topical treatment of simple dermatological infections, but are unsuitable for systemic use. The above does, however, not apply to all antibiotics and antiseptics and the information should be used with caution.

4.2.2 Bacterial diseases

Primary pyoderma is usually caused by either *Staphylococcus aureus* or *Streptococcus pyogenes*, or both. In contrast, secondary pyoderma can be caused by many types of bacteria when a primary lesion is present. In secondary pyoderma, both *S. aureus* and *S. pyogenes* are frequently found.

In temperate climate zones and under good hygienic conditions *S. aureus* is usually found in pyoderma, as it is a normal commensal on the human skin. *S. pyogenes* is generally not found on the human skin, as it cannot easily survive on the healthy skin. At higher temperatures, higher humidity, or poorer hygienic circumstances – conditions which are often present in the least developed regions – *S. pyogenes* is more generally found in primary and secondary pyodermas (1-3). *S. pyogenes* is more dangerous than *S. aureus*, because it generally causes deeper infections, and in approx. 1% of the cases complications such as endocarditis and nephritis occur (4). To prevent these complications, some authors recommend treating each *S. pyogenes* pyoderma infection systemically with antibiotics.

4.2.3 Antimicrobial treatment

Bacterial skin infections can be treated topically with antibiotics or antiseptics, or systemically with antibiotics (burns present a special case and are dealt with separately in paragraph 4.3). Both routes of

administration have advantages and drawbacks. Points to consider are the penetration of the antibiotic into the actual site of infection, hypersensitivity, bacterial resistance, and benefit/risk- and benefit/cost ratios.

One of the advantages of local, topical treatment is that high concentrations can be achieved at the site of infection without inducing systemic side effects. This may be true in some cases, but not in all. First, a high concentration at the infection site may not be achieved when crusts or pus prevent the drug from reaching its site of action. Second, the absence of risks of systemic side effects after topical application of antibiotics is subject to discussion. Such side effects have been frequently reported, for example loss of hearing after local use of aminoglycosides. These side effects, however, tend to be milder than following systemic treatment. Systemic antibiotic treatment usually results in sufficient concentration at the infection site, except in specific cases such as extensive deep burns (see paragraph 4.3).

The disadvantages of topical use of antibiotics are many. Hypersensitivity may develop from both systemic and topical application, but develops more rapidly after topical use. This is highly unwanted as it can prohibit future systemic use of these antibiotics in life threatening situations. Some of the antibiotics that are frequently used on the skin can also be life-saving drugs. Cross sensitivity can prevent further use of a complete group of antibiotics (e.g., aminoglycosides). This has led to a general consensus that certain antibiotics, such as penicillins and sulphonamides should never be used on the skin (2). There is still discussion about the aminoglycosides, but it can be concluded that use of these potentially life-saving drugs on the skin should be kept to a minimum. Leyden and Kligman argue that the prevalence of hypersensitivity to neomycin, which belongs to the class of aminoglycosides, should not be exaggerated (2). Neomycin was once used on a large scale in antiperspirants, which did not lead to as many hypersensitivity problems as expected. However, De Groot argues that reactions to cosmetics are generally underreported (5).

Resistance develops much more rapidly when antibiotics are used on the skin, as compared to systemic use. This is related to the presence of large numbers of bacteria and viruses on the skin, particularly in skin infections, and fluctuating concentrations of the antibiotic. This situation actually promotes bacterial resistance by selection. Large numbers of bacteria and viruses form an ideal situation for the transduction of resistance. Transduction is the transport of bacterial DNA plasmid material from one bacterium to another by virus infection. Extensive use of antibiotics on the skin can thus lead to multiresistant bacteria leaving life threatening infections untreatable. Cross resistance between similar antibiotics is generally a problem.

With respect to the balance in therapeutic and side effects following topical or systemic treatment the differences are not so clear. Antibiotics that are applied on the skin will be absorbed, at least to a certain extent, and systemic treatment may result in considerable concentrations in the skin (e.g., tetracyclines). The better penetration of systemic treatment into deep infections is one of its main advantages. On the other hand, newer topical antibiotics have been shown to be highly effective for example in impetigo (6). However, these preparations are expensive and therefore of limited value to tropical dermatology in the least developed regions. The risk of therapeutic failures should be avoided, as in the least developed regions people often have to travel a long way to reach a doctor and should be spared a second voyage whenever possible.

Our weighing of the therapeutic advantages and disadvantages of topical use of antibiotics leads to the conclusion that there is no place for skin treatment with antibiotic drugs that are either reported to be sensitising, or considered essential for systemic treatment. This conclusion extends to include all antibiotics

within the same group, or with the same mechanism of action. As a consequence, local treatment with aminoglycosides, such as neomycin, should be dismissed as well.

From a pharmaceutical point of view systemic antibiotics are also preferred. Most antibiotics are unstable chemicals. Due to the presence of water they have a limited shelf life in dermatological preparations. Antibiotics in tablets are generally more stable, as they contain no water. Also, the transport of tablets is easier and cheaper, which is an important aspect for health care in the least developed regions.

At this point, two choices need to be made regarding the treatment of bacterial skin diseases: 1) the route of administration, topical or systemic, and 2) the choice of the active ingredient, antibiotic or antiseptic. Topical treatment is useful in uncomplicated, superficial skin infections, and antibiotics should not be used in these cases; simple antiseptics will do. Serious skin infections need to be treated with systemic antibiotics, which can be administered orally or intramuscular by injection. In first line dermatology care there is no place for routine topical antibiotics. The only exceptions to this rule are the treatment of extended deep burns, and possibly the short-term treatment of infected eczema.

4.2.4 Antibiotics

We discourage the use of topical antibiotics in first line dermatology in tropical less developed regions. Despite this viewpoint, we discuss the main concerns and issues in this paragraph, as their use may be common practice in tropical countries.

An antibiotic that is to be used in topical therapy must fulfil the following requirements:
- the spectrum of activity must include the relevant pathogenic species;
- it must be stable in non-occlusive dermatological preparations;
- the incidence of bacterial resistance must be low;
- it must be non-sensitising, as sensitisation may preclude its use for the same individual in life threatening situations.

The following (groups of) antibiotics have gained acceptance as antimicrobial drugs for the skin.

Tetracycline is active after both topical and oral use, and it is generally well tolerated. In the presence of water it is unstable; the shelf life of tetracyclines in aqueous solutions is limited to 24 hours at 20 °C. The decomposition products of tetracyclines are toxic. Tetracycline is excreted through the skin after oral administration. A major problem in tropical countries is the risk of photosensitivity. Adequate protection against sunlight is essential when this complication develops. Topical use of tetracycline is not feasible in the tropics, but there may be a place for oral tetracyclines in severe acne.

Chloramphenicol is an active, moderately sensitising, and reasonably stable antibiotic; solutions have a shelf life of 4 months at 20 °C. Its use should be limited to life threatening situations because of the risk of bone marrow depression. This side effect is seen in two forms, one that is dose related and reversible, and another that is not dose related and irreversible. The latter usually results in fatal aplastic anaemia. When chloramphenicol is used on the skin, the risk of dose related bone marrow depression will be minimal, but the risk of non-dose related severe aplastic anaemia is similar to oral use. Chloramphenicol is a life-saving drug in meningitis and should be reserved for this indication. Thus, it should not be used for trivial skin infections.

Neomycin is active in skin infections, but is has a relatively small spectrum of action. As it is relatively non-toxic to streptococci, it should be combined with other antibiotics, such as bacitracin. Neomycin is stable, and aqueous solutions have a shelf life of 1 year at 20 °C. Hypersensitivity is not uncommon. This is important as cross sensitivity to other aminoglycosides is expected. Systemic side effects such as hearing loss following the local use of aminoglycosides may occur.

Bacitracin is generally combined with neomycin. The combination is active against streptococci. Bacitracin is generally well tolerated but unstable, in aqueous solutions it should not be kept in store for more than 48 hours. It can only be used in water free preparations, and even those should be kept cool. It has no place in tropical dermatology.

Gentamicin has the same general properties as neomycin. It could have a very limited place in local therapy for the treatment of heavily contaminated extensive deep burns that do not respond to silver nitrate or silver sulfadiazine (see paragraph 4.3).

Erythromycin and clindamycin are small spectrum antibiotics that are generally well tolerated and have a place in acne therapy in developed countries. Their usefulness in tropical regions is limited as a result of their instability in the presence of water, and their high cost. They are used systemically for serious diseases, and should not be used for topical therapy.

Fusidic acid is another antibiotic that is unstable in the presence of water. Its therapeutic activity declines in the presence of blood and pus. It can be used for staphylococci that are resistant to many other antibiotics. However, staphylococci rapidly acquire, but also loose resistance to fusidic acid. As in the least developed regions the main problem is not staphylococci but streptococci, there is only limited place for fusidic acid.

Mupirocin is another antibiotic that is used in infections with resistant staphylococci and streptococci. It can only be used locally because it is very quickly eliminated from the body after systemic use. Mupirocin is relatively expensive and has a limited indication, but could be considered a second line treatment for serious infections caused by susceptible organisms. In impetigo it was shown to be superior to oral antibiotics (6).

Taken together, we consider none of these antibiotics suitable for routine use in topical therapy in the least developed regions. The neomycin/bacitracin preparation that was previously on the Essential Drugs List of the World Health Organization (WHO), is not included in this formulary because we consider neomycin too sensitising and bacitracin not stable enough. If topical treatment needs to be given, the choice should be an antiseptic. In systemic infections and for the treatment of skin infections, there is a place for systemic antibiotics. Further elaboration of this topic is beyond the scope of this book, because rational drug treatment with systemic antibiotics should be part of a coherent antibiotic policy that aims at minimising the development of resistance.

4.2.5 Antiseptics

Antiseptics differ in some aspects from the antibiotics described above. One of the important differences is that resistance develops against practically all antibiotics, whereas in the case of antiseptics resistance only develops against a few preparations. Thus, the reduced risk of resistance development can be an important advantage of choosing an antiseptic. In this paragraph we discuss characteristics of various antiseptics.

Chlorhexidine is relatively cheap and well tolerated. It has a quick onset of action, with residual activity. It is also active in the presence of blood and pus, and is non-toxic to human cells. Although there is one report on delayed wound healing in rats that were treated with chlorhexidine, recent research did not reveal such negative effects (7). Resistance against chlorhexidine is increasing in the developed world, where infections with resistant micro-organisms are a great problem, especially in hospitals.

Chlorhexidine is reasonably stable but its decomposition products are toxic (see paragraph 9.3). These may cause hypersensitivity reactions. Chlorhexidine is available in various salt derivatives. Chlorhexidine digluconate can only be used as a solution. The 20% concentrate is a better choice than the 5% solution that is included in the WHO Essential Drugs List, because the latter also contains a detergent and a colouring agent. From a therapeutic point of view these additions are not necessary, but may cause side effects. In addition, transport of a 20% solution is more efficient and cheaper. For use in tropical countries, chlorhexidine diacetate may be more appropriate because it is available as a powder. In the absence of water it is more stable, as hydrolysis will be minimal. Chlorhexidine diacetate can be dissolved when needed. Concentrated stock solutions of chlorhexidine diacetate cannot be prepared because the limit of solubility is close to the recommended concentration for use. The choice of either chlorhexidine digluconate or chlorhexidine diacetate will depend on the local situation and the health care system.

Cetrimide is both an antiseptic and a detergent. It is generally combined with chlorhexidine as the combination has a better activity and the risk of resistance development is smaller. It is generally well tolerated but allergic and necrotic skin reactions have been reported after repeated use. Cetrimide should therefore not be used for long-term treatment or as a routine antiseptic.

Iodine has a good antiseptic activity and a quick onset of action, works against bacterial spores and viruses, but it is unstable and expensive. It also stings and stains. Iodine can be absorbed and frequent use or application on large parts of the body should be avoided, as the iodine may influence the thyroid function. Resistance to iodine is unlikely to develop. Povidone iodine (betadine) has better characteristics but is more expensive. Stability of povidone iodine is limited as the iodine is liberated at temperatures above 43 °C.

Chlorine and chlorine releasing preparations have been used extensively as antiseptics. They are still in use for technical disinfection in western countries. Their value as routine antiseptics is limited. Chlorinated lime and hypochlorite solutions are cheap and effective antiseptics. Resistance is unlikely to develop. Hypochlorites are most active in slightly acidic solutions, but they are only stable in alkaline solutions. Solutions should thus be freshly prepared from powders or from concentrated alkaline stock solutions. Hypochlorites may cause dissolution of blood clots and bleeding. Hypochlorites are rapidly inactivated by organic material. For stability reasons, the solution has a high alkalinity.

Potassium permanganate is cheap, has a quick onset of action and resistance is unlikely to develop. The solution is inactivated by all kinds of organic materials, including blood, pus, cotton swabs that are used to apply the solution, and the skin itself. Hence it is very short-acting. It cannot be kept as a diluted solution as it is very unstable, but is easily prepared from stock solution. As it dissolves slowly and crystals or strong concentrations cause severe chemical burns on the skin, it is best to dispense a stock solution instead of the crystals. Potassium permanganate is very useful for antiseptic bathing, for which mild antiseptic and astringent properties are combined. Antiseptic bathing with potassium permanganate also reduces the foul smell from infected wounds.

Silver nitrate is expensive. It is potent, non-sensitising and well tolerated, but it has a very narrow therapeutic window: 0.1% is ineffective, 0.5% is effective and 1.0% is toxic (8). When used on large parts of the body, as may be the case for the treatment of extensive burns, it may cause hypochloremia due to precipitation of silver chloride in tissue. Silver nitrate stains skin and clothes. Silver nitrate is useful for primary care treatment of burns and leg ulcers. The treatment of burns is dealt with separately in paragraph 4.3.

Gentian violet and other triphenylmethane dyes are used for pyodermas caused by streptococci and staphylococci, and for *Candida* infections of skin, mouth (thrush) and vagina. The solution stains. When used on wounds the stains may be permanent. Therefore, it should not be used on wounds and preferably not in the face. A 1% gentian violet solution was included in the WHO Essential Drugs List until 2011. It is generally considered to be well tolerated, although Meurer reported necrotic reactions, especially when the 1% solution was used in intertriginous regions of the body, such as skin folds. He suggested using more diluted solutions (9). In an in vitro investigation we found gentian violet to be active against streptococci of groups A and B at concentrations far below 0.5% (10). These streptococci are the ones generally found in skin infections. The activity of gentian violet against *Candida albicans* and *Staphylococcus aureus* was even better. The activity against Gram negative organisms was more variable, with *Pseudomonas aeruginosa* showing the lowest level of sensitivity to gentian violet. The addition of brilliant green only had a slightly positive effect. The minimal effective concentration of gentian violet remained far below 0.5% and we therefore conclude that this concentration is appropriate (10).

To gentian violet related triphenylmethane dyes are suspected carcinogens (11). Although this issue has not been resolved yet, Diamante and co-authors do not recommend using gentian violet and related dyes in cosmetic preparations. For this reason, the expert committee of the WHO Essential Drugs List 2011 decided to remove it from the list as there are sufficient alternatives. Based on this advice we recommend the use of either chlorhexidine or povidone iodine as a first choice antiseptic for the local treatment of pyoderma. We kept gentian violet in this formulary, specifically for the treatment of *Candida* infections on the skin and as an alternative treatment for pyoderma, since it has been used extensively with excellent results as a general antiseptic, even under a corticosteroid ointment. Its drying effects may have contributed to these results (12).

Sulphur has been used extensively in dermatology because of its keratolytic, antiseborrheic, and antimicrobial effects, although the latter has not been fully substantiated. Sulphur is still in use for the treatment of acne, seborrheic dermatitis, scabies and tinea versicolor (13). Recent literature is scarce. Sulphur is non-toxic and safe in normal use, even in small children (13). Several hypotheses are mentioned in the literature to explain the antimicrobial effect of sulphur. One is that it depends on the conversion of sulphur to pentathionic acid by the normal skin flora or by keratinocytes. This mechanism has only been studied in plant disease models. The supposedly active substance, pentathionic acid, is known in inorganic chemistry. It is an unstable free acid that breaks down rapidly into sulphur and sulphur dioxide. The pentathionate ion is slightly more stable. In vitro investigations are difficult to perform and should be aimed at forming the active compound(s) in situ. A second hypothesis claims that the formation of hydrogen sulphide plays a role in the antimicrobial effects of sulphur, a conversion that is also expected to take place on the human skin by keratinocytes (13).

We tested the in vitro growth inhibitory effects of sulphur on several micro-organisms (*S. aureus*, group A and B streptococci, *C. albicans*) (12). We found no growth inhibition in a culture of normal human skin flora. In none of these cultures the characteristic odour of hydrogen sulphide was observed. On an agar medium, heavily inoculated with normal human skin flora and mixed with sulphur, growth of *S. aureus* was

not inhibited as compared to growth of this same organism on the same medium without sulphur added, and with the same human skin inoculum. This human skin flora was unable to produce from the sulphur any substance toxic to *S. aureus*. We developed this in vitro model to investigate the antimicrobial effects of sulphur, as we did not find one in the literature. Another way to test the microbial effects of sulphur is obviously by clinical investigation. Such studies using sulphur alone (as an antiseptic) were not found in the literature (13). Sulphur is still used in dermatology and good results are claimed, but usually in combination therapy. Therefore, no conclusions about the antimicrobial effectiveness of sulphur can be drawn from these publications (14,15).

Keratolytic agents usually have some effect in superficial infectious skin diseases, because they accelerate the elimination of diseased parts of the horny layer. Some remarks concerning these effects of sulphur are:
- There is an effect on keratinisation.
- Keratolytic agents (e.g., salicylic acid) are effective in acne, seborrheic dermatitis and dermatomycoses. In scabies a positive effect of keratolytics is to be expected.
- On human skin hydrogen sulphide is thought to be formed, which is toxic to some organisms (e.g., *Sarcoptes scabiei*). The formation of hydrogen sulphide seems to depend on the presence of keratinocytes and has not been observed in vitro. It is claimed to have antiseborrheic properties.

Regarding the therapeutic effects of sulphur the following conclusions are drawn.
a. An antimicrobial effect of sulphur cannot be proven in an in vitro test.
b. Sulphur should be tested clinically, by comparing it to placebo and keratolytics such as salicylic acid. There are no publications available on such investigations.
c. An anti-infective effect of sulphur is expected but may be due to its keratolytic action alone. In this case there is no place for sulphur on an essential drugs list; salicylic acid is the drug of choice.
d. An antiseborrheic effect of sulphur similar to ketoconazole has been found.

4.2.6 Conclusions

Superficial skin infections can be treated with topical anti-infectives; in general antiseptics are the most appropriate choice. Antibiotic treatment should be avoided in trivial infections to prevent the development of bacterial resistance. This applies to both local and systemic treatment. Extensive skin infections should be treated with systemic antibiotics, except burns.

For primary health care, chlorhexidine or povidone iodine preparations are most appropriate for treatment of skin infections. They are also used as surgical antiseptics. Surgical antiseptics are, in contrast to antiseptics for skin infections, not intended to stay on the surface for longer periods of times, and must be fast acting. Both drugs, chlorhexidine or povidone iodine, meet this criterion. Povidone iodine has a somewhat broader spectrum of action, and is not prone to resistance development.

Potassium permanganate and gentian violet are suitable alternatives to chlorhexidine and povidone iodine for use in primary health care. For safety reasons potassium permanganate should be kept in a stock solution requiring dilution immediately before use. Gentian violet should be used as a 0.5% solution. It should be available to the village health worker as a powder for solution. As a powder gentian violet is easily transportable and stable.

4.3 Treatment of burns

4.3.1 Introduction

Burns are classified as partial thickness burns and full thickness burns. In partial thickness burns the skin is only partially destroyed. Skin functions are still present to some extent, such as blood vessels delivering blood with nutrients, immune factors, etc. As a result, the damaged skin has repair potential. As the nerves are functioning there is pain. In full thickness burns all skin functions are destroyed and no pain is felt. No spontaneous repair is possible and immune responses are lacking, which is a serious condition. In cases that very small areas are destroyed by full thickness burns, the situation is less dangerous as some skin functions can be maintained from adjacent healthy skin. Repair function from vital surrounding skin is only possible in very small full thickness wounds.

Treatment of full thickness burns is different from that of other wounds and partial thickness burns. Systemic complications and other problems lead to high mortality rates. Some authors advocate the use of routine systemic antibiotic prophylaxis (16). They argue that burn patients typically have impaired systemic immune responses and general infections such as pneumonia are a main cause of death. However, the available evidence for such treatment is weak.

Surgical techniques are necessary for repair of the burn wound area. There is no local immune response and systemic antibiotics will not reach the site of action, rendering infections difficult to treat. The treatment of burns is preferably done in specialised burn care centres, but these are not always available.

As treatment of local infections is practically impossible, the prevention of infection is essential. The only way to achieve this is by local application of anti-infectives. The treatment aim is to keep the burn wound sterile. Infection makes skin transplantation practically impossible, as transplants are usually rejected in the presence of micro-organisms. As a consequence, appropriate measures for infection prevention should be available at primary care facilities and health workers should be able to start these immediately.

4.3.2 Preparations for burn treatment

Synthetic skin substitutes such as Duoderm® (polyurethane and hydrocolloids) or Opsite® (polyurethane) have a place in burn treatment (17). They promote wound healing by creating a favourable humid wound environment and form an artificial physical barrier against micro-organisms. Skin substitutes can be left in place for longer periods of time. There is considerable market pressure from manufacturers to promote the use of these materials (11).

Mafenide acetate is used as a cream containing 11.2% of the active ingredient. A 0.5% cream and gauze dressings saturated with the 5% solution have also been used (17). Mafenide acetate has a broad spectrum of action and is active in the presence of blood and pus. Mafenide is absorbed and inhibits carbonic acid anhydrase, thereby causing acidosis and hyperventilation. Therefore, mafenide acetate should not be used if any respiratory complications are present. Mafenide is a sulphonamide and relatively often causes hypersensitivity and pain when applied. On absorption it may cause the general sulphonamide side effects, such as nausea, headache and dizziness. Due to these potential side effects mafenide is of limited value, especially in resource scarce regions. Mafenide inhibits the rejection of necrotic tissue. Necrotic tissue needs to be removed for proper wound care. The inhibitory effect is thought to be generally linked to anti-microbial activity, not specifically to the effect of mafenide, as it is seen with other anti-infectives as well (18). Resistance against mafenide develops but its relevance in normal clinical practice is uncertain.

Silver nitrate solution is used with compresses. Silver nitrate creams were found to be less effective (18,19). Silver nitrate has a very narrow therapeutic window. In the preferred concentration of 0.5% silver nitrate does not inhibit human cells and wound repair (8). Silver nitrate therapy should be started as soon as possible as it has a preventive, rather than a curative effect. Compresses should be kept wet at all times and good wound care is essential. Rejection of necrotic tissue is inhibited. Silver nitrate in solution has a limited shelf life, but solutions can be easily prepared when appropriate measures and materials are available to ensure the right concentration. Silver nitrate solutions are self-sterilising. If clean water is used for the preparation of silver nitrate solutions, they need not be sterilised. Advantages of silver nitrate are a broad spectrum of action, no relevant resistance problems, no sensitisation, and painless application. Disadvantages are the risk of electrolyte disturbances due to the reaction of silver with chloride, and staining, which can be a serious problem. Staining makes wound care more difficult as it complicates the distinction between necrotic and living tissues (18). In rare cases infection with nitrate reducing micro-organisms has led to methaemoglobinaemia.

Silver sulfadiazine is used as a sterile cream. The silver ion is bound to the molecule and the drug therefore lacks some of the disadvantages of silver nitrate solution. There is no risk of electrolyte disturbances when silver sulfadiazine is used, and methaemoglobinaemia does not occur. Also staining is not a problem. Silver sulfadiazine is included in the WHO Essential Drugs List for the treatment of burns. It does not penetrate into the wound and therapy is aimed at prevention rather than treatment of infections. Silver sulfadiazine inhibits, like the other drugs, the rejection of necrotic tissue. Application is painless and the antimicrobial spectrum is broad. Compared to silver nitrate it is less effective against *Proteus* and *Pseudomonas* species, but more effective against coliform Gram negatives. Resistance against silver sulfadiazine is more likely to develop and has been reported quite often (19,20). Silver sulfadiazine has been shown to be cytotoxic (21), but so are most of the other antimicrobial agents that are used for burn wounds. A major drawback of silver sulfadiazine cream is its physical and chemical instability. The preferred storage temperature is below 25 °C. We demonstrated physical instability at 40 °C. As a consequence silver sulfadiazine cream is unsuitable for primary care in tropical countries. There may be a place for commercially available silver sulfadiazine cream in hospitals. Silver sulfadiazine is sometimes combined with cerium nitrate in creams. Burnt skin produces lipid protein complexes that impair immunological responses. Cerium nitrate prevents this by denaturation of these lipid-protein complexes (22).

Silver exerts its antimicrobial action in its ion state of Ag^+. A number of modern wound materials contain silver in a slow release system. Examples of these are Acticoat®, Aquacel-Ag® and Silvercel®. These products have shown good results in burn wound treatment (23,24). Their unit price is rather high but as they don't need frequent dressing changes they may actually be cost effective.

Gentamicin is used for the treatment of burns that were infected by a variety of micro-organisms. It is more effective in creams than in ointments. Some of the gentamicin penetrates through the wound, making treatment of an established infection possible. However, gentamicin has serious drawbacks. It is absorbed into the body, and may cause damage to the hearing system and impaired renal function. Both side effects are dose related and occur occasionally when the cream is used on large parts of the skin. Gentamicin cream is expensive. Bacterial resistance, especially against *Pseudomonas* and *Proteus* species, occurs widely as the result of large scale local use of aminoglycosides. Sensitisation reactions are not uncommon. Other antibiotics such as bacitracin, neomycin and polymyxin B are often used in combinations with aminoglycosides.

Mupirocin is used for burn wounds when MRSA (multiresistant *Staphylococcus aureus*) has become a problem. It can be of value in specialised burn care units in rotation schemes with other antimicrobial agents, but has no place in primary care (17) .

Povidone iodine solution or ointment has been used in burn care (25). It has a good activity, but application is painful and systemic side effects, such as impairment of the thyroid function, are to be expected. Iodine can inhibit proliferation of human cells and tissue repair. Resistance has never been observed. Most authors consider iodine or povidone iodine to be unsuitable for large wounds (>20% of the body surface) because of local and systemic side effects, but it may be useful for routine treatment of smaller (burn) wounds.

Chlorhexidine has been studied for burn wound treatment. A 2% cream of chlorhexidine diphosphanilate was found comparably effective as silver sulfadiazine in a rat model on *Pseudomonas aeruginosa* and *Proteus mirabilis* (26). Chlorhexidine was also tested clinically (27). An earlier publication was less positive about chlorhexidine because application can be painful and there are concerns about the development of resistance, especially against *Pseudomonas* species (28). Chlorhexidine preparations may be of use in the primary care treatment of burns.

Several natural products are traditionally used on burn wounds and some have been investigated. Honey has antimicrobial activity due to its high osmolarity and the formation of hydrogen peroxide. In a clinical trial that compared honey to potato peel dressing both were found to be effective (29). Papaya pulp is used in The Gambia as a burn dressing (30). The mashed pulp is applied to the wound. This appears to be effective. Possible mechanisms of action include proteolytic enzyme activity and antimicrobial activity. In Malaŵi a mixture of honey and ghee (a type of butter made from buffalo milk) is used for burn wounds, apparently with good results (31).

4.3.3 Conclusions

The treatment of burns, especially in large full thickness burns, aims at preventing infection. To keep the wound free from infection, treatment of extensive full thickness burns should be initiated as soon as possible. A preparation for infection prevention needs to be available in primary care facilities at the village. There are no ideal preparations for primary care treatment; the choice depends on the local situation. A generally available antiseptic of choice, such as chlorhexidine or povidone iodine, can be used. Honey or similar preparations can also be useful.

Severely burned patients need to be transported to a hospital whenever possible for adequate treatment. At the hospital silver nitrate solution, silver sulfadiazine cream, or other preparations are suitable, provided they can be stored at temperatures below 25 °C. Very small or partial thickness infected burns (pain present) can be treated systemically. The prevention of infection is not crucial for these burns.

Local production of creams or ointments for the treatment of burns should be carried out in a clean environment to limit contamination with micro-organisms. This is difficult in small, poorly equipped production units. Silver nitrate solutions are sterile if clean water is used for preparation. Hence, these solutions are suitable for preparation in small scale production units.

4.4 Treatment of ulcers in leprosy

4.4.1 Introduction

In the management of ulcers of any type it is important to establish the causes of the ulceration. If possible, ulcer treatment is combined with measures to acquire and keep healthy granulation tissue in the base of the ulcer. During this period, care is taken not to disturb the natural healing process. Adequate rest is essential for wound healing.

Leprosy is the classic example of a disease which is often complicated by permanent nerve damage. Importantly, permanent nerve damage caused by any other disease will lead to similar problems as in leprosy, and need similar care. In case of recurrent ulceration always try to find and treat the underlying condition. If leprosy is suspected, the patient in the first place needs adequate treatment for this condition. In many regions this is done in specialised leprosy care centres.

The management of dry skin is essential to prevent secondary skin defects in leprosy, which is discussed in paragraph 4.9.4. This paragraph deals with the prevention and treatment of ulceration.

Brand and Fritschi gave an excellent overview of four different causes of tissue damage in insensitive limbs: (1) direct damage by high stress or burns; (2) ischemic necrosis from continuous pressure; (3) repetitive moderate stress; (4) mechanical stress on infected tissue. They emphasise that people with nerve damage who experience no pain sensation, continue to use a wounded or infected limb and subject it to stress in spite of the infection. As this is the main cause of the loss of fingers and destruction of feet in leprosy, it is extremely important to teach patients that the only way to avoid permanent deformity and disability is to rest the wounded part of the body until it heals (32).

Preventive measures are very important (32-34), but once an ulcer has formed, measures need to be taken to acquire healthy granulation tissue in the base of the ulcer. Rest is essential for the diseased part of the skin, especially when a secondary infection and oedema are present. Oedematous limbs should be rested in a position above the level of the heart (left shoulder) with a free unpinched outflow.

4.4.2 Treatment

Fissures or deep cracks that were formed in the skin act as entry spots for infections. The callous skin around fissures should only be removed mechanically with a sterile instrument. The depths of the crack can be painted once daily with a 0.5% solution of gentian violet in water (33) or with the antiseptic of local choice. If an abscess exists, it should be opened widely to allow free outflow of pus. Any necrotic tissue parts should be removed meticulously. Minor infections may respond to rest and twice daily soakings with diluted potassium permanganate solution during fifteen minutes, or cleaning in a bucket with water and soap (34). The extremely foul smelling of some ulcers responds quickly to soakings with a sterile solution of 1% metronidazole in 0.6% saline, or systemic use of metronidazole. The literature on the efficacy of topical metronidazole is conflicting. Therefore we did not include this preparation in the formulary. More serious infections need systemic antibiotics in addition to local treatment. If possible, the choice of the antibiotic course should be based on the results of a culture and sensitivity test of the micro-organisms causing the infection. The formation of granulation tissue is enhanced by daily application of povidone iodine powder or possibly phenytoin in the ulcer (35). Once healthy granulation tissue has been formed in the base of the ulcer, rest is no longer necessary provided the natural process remains undisturbed.

The use of zinc adhesive plaster is advocated on cracks and wounds. It prevents pressure, gives a moist environment, and prevents dirt to come in. Zinc is believed to prevent bacterial growth and enhances wound healing (12).

If ulcers of the feet and lower legs are complicated by lymphedema, pressure bandages are needed to reduce oedema formation. In case of a plantar ulcer excellent results are expected with the application of a below knee total-contact plaster cast (32). Old fashioned gypsum casts have been shown to be superior to the non-absorbing modern artificial ones. Clean ulcers in other areas can be dressed with zinc paste or with a zinc-impregnated bandage once in 1 to 7 days, depending on the amount of secretion. Epithelialisation over healthy granulation tissue may enhance by a variety of expensive semipermeable hydrocolloid occlusive dressings (36). Preventive measures should be taught and practised throughout the healing process. For people with plantar ulcers protective footwear should be made available before the ulcer is healed (32).

4.5 Mycotic skin infections

4.5.1 Introduction

Skin mycoses can be either deep or superficial. Both are more common in tropical countries than in temperate climates. Pityriasis versicolor for example, develops under conditions of high humidity and temperature and is far more common in tropical countries than in temperate zones (37).

Superficial mycoses of the skin are treated adequately with simple topical medicaments and do not require systemic treatment. Such topical preparations are cheap and safe in contrast to systemic treatment that may also cause serious side effects.

4.5.2 Antimycotics: time honoured preparations

Whitfield's ointment used to contain salicylic acid 6% and benzoic acid 12%. It caused many side effects, sensitisation and/or irritation reactions. Lower doses are used nowadays, e.g., 6% benzoic acid and 3% salicylic acid in the UK, and 5%-5% in the Netherlands. Side effects and sensitisation have subsequently reduced. The activity of salicylic acid is thought to result from its keratolytic effect. This effect is more pronounced with 5% than with 3%, which is an argument for using 5% salicylic acid in Whitfield's ointment. Whitfield is active against dermatophytes but not against *Candida* species.

The emulsifying ointment formulation of Whitfield's ointment is reported to be more effective than the petrolatum formulation (38). This is to be expected, as potentiation of antimycotics by sodium lauryl sulphate, the emulsifier of emulsifying ointment, has been documented (39). Whitfield can also be prepared as a cream and some authors consider this preparation to be somewhat more active (except on the feet). This higher activity is explained by better liberation of the active ingredients from the cream as compared to the ointment. Also, the drying effect of the cream is advantageous. On the other hand, Logan and co-workers could not detect any difference in activity between the ointment and cream, but their patients preferred the cream (40). In our opinion the choice for either 6%-3% or 5%-5% depends on local preference, as does the choice for cream or emulsifying ointment. Benzoic acid and salicylic acid in petrolatum (vaseline, soft paraffin) is less preferred as it seems to be less effective, is occlusive and cannot be washed away.

The Whitfield's cream as formulated in this book, has been compared with clotrimazole cream in a double-blind trial involving 153 patients with a dermatophyte infection of the skin in Karonga District, Northern Malaŵi, including 25 patients who were HIV-1 seropositive. The vast majority of patients with a dermatophyte infection of the skin, including the HIV-1 seropositive patients, was cured with either topical antimycotic preparation. Whitfield's cream and clotrimazole cream were both very effective. The lower cost makes Whitfield's cream the treatment of choice in dermatophyte infections of the skin in tropical primary health care (41). There is no place for expensive oral therapy.

Gentian violet is used for *Candida albicans* infections of the skin, mouth and vagina. Activity of gentian violet in such infections is reported in the literature and was seen in our experiments (10,42). Other dyes are also used but gentian violet is the most suitable. Castellani's solution is considered obsolete. Fuchsine is a suspected carcinogen, boric acid is toxic and should not be used, and phenol and resorcinol are not considered the most appropriate local antimycotics.

Sodium thiosulphate is used for pityriasis versicolor (43). It is dispensed as crystals packed in suitable doses. For example in Africa most Coca Cola bottles have a capacity of 300 ml. Sodium thiosulphate can be packed in 30 g packages for dissolution at home in a Coca Cola bottle filled with water. Stability and preparation problems are minimal. Sodium thiosulphate is well tolerated and non-toxic, and very cheap.

Selenium sulphide is used for pityriasis versicolor, but local side effects may occur. These are prevented by applying oil, for example coconut oil, the next morning (12). Selenium sulphide is toxic on ingestion.

Clioquinol is not considered a drug of choice, neither for systemic nor topical use. It is not very effective against yeasts and its activity against dermatophytes is also limited. Upon topical use it is generally well tolerated but stains. Sensitisation and severe irritation were observed occasionally. Nowadays clioquinol is a controversial drug because it may cause severe neurological disorders, although this is unlikely to result from topical use. It is considered essential since more active and cheaper preparations are available, such as Whitfield's ointment and gentian violet solution.

Tolnaftate is used as an antimycotic agent. It may have a somewhat quicker onset of action than Whitfield's ointment, but is more expensive. In the Netherlands it is only used in combinations. Such combinations are equally expensive as miconazole cream, but ineffective against *Candida* species and slower acting than miconazole. There seems to be no place for preparations with tolnaftate.

Undecylenic acid is only a weak antimycotic, and quite expensive. There is no place for undecylenic acid on an essential drugs list.

4.5.3 Antimycotics: newer preparations

The imidazoles (miconazole, ketoconazole, itraconazole) belong to a newer generation of antimycotics. They have a broad spectrum of action against dermatophytes, *Candida* species and some bacteria, are non-toxic, but usually more expensive than the first choice time-honoured preparations. As compared to the older antimycotic preparations like Whitfield's ointment, the onset of action of the new generation antimycotics is faster, but they are equally effective (41). In general, there are only minor differences between the imidazoles for local use (42, 43). Only miconazole has obvious antibacterial activity (12). Miconazole is the preferred imidazole preparation because it is widely known and prices have gone down as patents ran out and more

preparations became available. For systemic use there are more differences between the imidazoles. Some are unavailable for systemic use and their side effect profiles differ.

Terbinafine is a broad spectrum antimycotic that is also active against *Candida* species. It is used both systemically and topically. Topical preparations are well tolerated and effective. The WHO has included a 1% topical preparation (cream or ointment) in the 2011 edition of the Essential Drugs List (44).

4.5.4 Antibiotics for antimycotic use

Nystatin is an effective antibiotic for *C. albicans* infections but is extremely unstable. It is equally effective as miconazole and other imidazoles (43). Nystatin can be used in topical preparations but systemic use is impossible because it is not absorbed. Amphotericin B is used systemically. Both antibiotics are unstable. Nystatin can only be kept for 6 months when stored in the absence of water and below 5 °C. These antimycotic agents are thus not suitable for use in primary care but are valuable for specialised hospital care.

Griseofulvin can only be used orally. It is used in dermatophyte infections of hair and nails and in widespread dermatophyte infections of the skin. It is ineffective against yeast infections. It is expensive, but cheaper than other oral medication. Photosensitisation has been described but is extremely rare.

4.5.5 Conclusion

In dermatophytosis we consider Whitfield's ointment or cream the drug of choice for primary health care. The risk of sensitisation is considered very small.

In superficial infections of *C. albicans* miconazole is the drug of choice. Gentian violet solution is an alternative. In pityriasis versicolor sodium thiosulphate or selenium sulphide are the drugs of choice. Sodium thiosulphate can be dispensed in 30 g packets with instructions how to prepare the solution.

Complicated or non-responding cases of dermatomycoses can be treated with topical terbinafine or miconazole. Systemic drugs are used in certain cases of extensive or deep mycoses. We advise to use the drugs on the most recent WHO Essential Drugs List (44). The 2011 edition includes griseofulvin and fluconazole. Miconazole cream is stable and suitable for the tropics.

There is little need for another antimycotic for topical use. Nystatin is useful in well-equipped hospitals, but the limited shelf life and cooled storage requirements are practical barriers.

4.6 Scabies and other parasitic skin diseases

4.6.1 Introduction

Scabies is a cosmopolitan disease but due to socioeconomic factors the incidence is much higher in developing regions as compared to the developed world. At any given time the worldwide disease burden of scabies is about 300 million people (45). Scabies and lice infestations are contagious and transmitted by close contact. Treatment of all contacts is necessary to prevent re-infestation. Education is important to reduce or prevent frequent re-infestations. In the tropics scabies is frequently associated with superinfection of the lesions with bacteria. Nephritogenic group A streptococci are frequently isolated and of concern, because of their relation with post-streptococcal glomerulonephritis (46,47).

Larva migrans (creeping eruption) is a nematode infestation of the skin. The infestation is usually self-limiting as the larvae die after some time, usually within six months. Secondary infections may complicate the disease. In most parts of the world, larva migrans is not a common disease and we do not consider drugs for larva migrans essential in this formulary. If treatment for cutaneous larva migrans is necessary, oral ivermectin is considered to give the best results (48). Jiggers, ticks and guineaworms are removed by hand or any other simple method. In most regions people know how to do this; drug treatment is not necessary.

4.6.2 Scabicides

The widely used scabicides, oral ivermectin and local preparations of lindane, benzyl benzoate and permethrin, were recently reviewed (49). Permethrin is considered the most effective but commercially produced permethrin cream is very expensive in comparison to locally produced lindane or benzyl benzoate preparations. Oral ivermectin is expensive as well and not considered to be more effective than either lindane or benzyl benzoate. Lindane and benzyl benzoate are equally effective against scabies.

Lindane was widely used as agricultural and household insecticide. This has led to an abundance of literature on environmental toxicity of lindane and toxic effects in humans. In the 2009 UN Stockholm Convention on Persistent Organic Pollutants lindane was banned as an insecticide, and is now considered more or less obsolete in the western world. The Convention made an exemption for lindane as second line treatment in human pharmaceuticals to control head lice and scabies (UN 2009). This is regarded an important decision, because the older literature states that lindane is well tolerated and has little toxicity when used correctly (50-52). Dermatologists in the field consider lindane more effective than permethrin (12). For these reasons, lindane retains in this formulary.

A single application of a 1% lindane lotion, cream or ointment is generally sufficient for a total cure of scabies. Sensitisation to lindane is uncommon. Bathing before the application of a lindane preparation is not necessary and enhances absorption. It should therefore be avoided. Lindane treatment should not be repeated. As itch may persist for weeks after all the mites have been killed, good information is important and in some cases an antipruritic preparation is indicated.

While lindane is often effective after a single application, benzyl benzoate should be applied at least two times. Sensitisation has been observed but is uncommon. Benzyl benzoate is generally non-toxic. The lotion contains 25% of benzyl benzoate and is more expensive than 1% lindane lotion.

Both lindane and benzyl benzoate are used for the treatment of scabies and lice. Lindane can be diluted to a 0.1% preparation to be used against lice. In western countries due to previous widespread use of lindane, lice, and occasionally scabies mites have developed resistance. In areas where lindane is only used in dermatological preparations this will not be the case. In western countries malathion is used to treat lindane resistant lice. Malathion can be more acutely toxic to humans than lindane, and it is more expensive. It cannot be used against scabies as it does not penetrate the skin.

Sulphur is used for the treatment of scabies in small children and pregnant women. Repeated applications may be as effective as lindane or benzyl benzoate but clinical trials are still needed to confirm this (49-51,53). A 10% sulphur cream or ointment applied on seven consecutive evenings is considered effective against scabies.

Other scabicides such as crotamiton or DDT are generally more expensive and less effective than lindane, and are more toxic. Crotamiton frequently causes irritation, and sensitisation is not uncommon.

4.6.3 Conclusions

Lindane has become a controversial drug in scabies and lice treatment. In our opinion it can still be used and at present it is by far the cheapest effective drug for the treatment of scabies. Two of the authors of this book have many positive experiences with the treatment of scabies with lindane and it was decided to keep it in this formulary. Proper instruction on its use is, however, absolutely necessary. It should be applied only once and not repeated. It is used for small children as well as adults. A 1% cream preparation seems to be the most suitable. A 25% benzyl benzoate lotion is more expensive than lindane but possibly safer. International environmental concerns make benzyl benzoate our treatment of choice for scabies in countries where lindane is no longer available. Sulphur 10% cream or ointment is a safe and effective alternative for the treatment of scabies in children and pregnant women. Would permethrin cream become much cheaper and available for local production in the future, it could develop into the treatment of choice.

We do not consider drug treatment for lice necessary, as frequent hair combing and washing of clothes are generally effective measures against lice.

4.7 Corticosteroids

4.7.1 Introduction

Corticosteroids have general anti-inflammatory, antipruritic and antimitotic properties. This makes them useful for a great number of skin diseases such as eczema, psoriasis and many others. Corticosteroids inhibit both inflammation and immune responses, and are used in immune disorders. They should not be used in infectious diseases. Infections are considered a relative contraindication for corticosteroids. An exception can be made when inflammation plays an important role and corticosteroids are indicated even in the presence of an infection. Corticosteroids are administered by mouth, injection or locally on the skin. Only preparations for topical treatment of skin diseases should be used in primary care dermatology.

4.7.2 Side effects of corticosteroids

Topical corticosteroids exert local and systemic side effects. Systemic side effects occur after absorption of the steroid. Corticosteroids are effective due to penetration into the skin, and some absorption is therefore inevitable. Children have a relatively large skin surface compared to adults and systemic side effects are more likely to occur. Once systemically absorbed, corticosteroids interfere with the corticosteroid synthesis in the adrenal glands. Their endogenous production is inhibited and depletion of corticosteroid reserves may occur. This leads to decreased physical stress responses. When corticosteroid absorption takes place over extended periods of time, and especially when stronger steroids are used, the corticosteroid activity in the body may get too high. This causes metabolic effects, of which Cushing syndrome is widely known. In children growth retardation may result from extended use of corticosteroids.

Local side effects of topical use of corticosteroids include atrophy and striae. They result from the inhibition of collagen synthesis. Corticosteroids may change the clinical appearance of skin diseases, thereby hampering a diagnosis, or even making a diagnosis impossible. The masking of infections is a well-known

example. Hence, the rule is to make sound diagnoses before starting treatment with corticosteroids. When corticosteroids are used in the face, perioral dermatitis and acne may develop or aggravate.

All these side effects are inherent to using corticosteroids. Whether or not side effects occur depends on the strength of the steroid used and the amount of steroid absorbed (i.e., dose and duration of treatment).

Sensitisation to corticosteroids may occur but is very difficult to diagnose as the presentation of the reaction is changed by the steroid itself. Such reactions are therefore likely underreported in the literature. Sensitisation reactions may present as apparent aggravation of the treated skin condition, or as treatment failures. Sensitisation may be due to degradation products of corticosteroids rather than to the steroids themselves, but no sound evidence supports this hypothesis (see paragraph 9.5).

4.7.3 Weak and strong corticosteroids

Corticosteroids are generally classified according to their activity profile.

- Class 1, weak activity: hydrocortisone acetate, dexamethasone.
- Class 2, moderate activity: triamcinolone acetonide, clobetasone-17-butyrate.
- Class 3, strong activity: betamethasone-17-valerate, betamethasone dipropionate.
- Class 4, very strong activity: clobetasol-17-propionate.

This classification is only of limited value, because activity is not only determined by intrinsic characteristics of the various steroids, but also by the level of penetration upon application. Penetration in turn depends on many factors such as the formulation and the skin condition. Occlusion enhances penetration and hence the level of activity of the corticosteroid.

4.7.4 Selecting a corticosteroid

Selecting corticosteroids for tropical dermatology is difficult. Relevant selection criteria are the required level activity and the price. From a pharmaceutical point of view strong corticosteroids are more difficult to handle because of their toxicity, and preparing homogeneous dosage forms can be difficult. Some corticosteroid esters are unstable due to hydrolysis.

Weak corticosteroids can be combined with penetration enhancers like urea and salicylic acid to obtain stronger preparations. Such combination creams were reported as very effective. For example, hydrocortisone/urea was as effective as betamethasone-17-valerate in a clinical trial of patients with dry eczema (54). Such clinical trials (54,55) have not been performed for other skin diseases. Since a considerable effect of urea itself on dry eczema is expected, the conclusions of these trials cannot be generalised to other skin diseases. Hydrocortisone is less stable in the presence of urea or salicylic acid, which is a major disadvantage of the combination. Taken together, we conclude that there is no place for fixed combinations of corticosteroids (hydrocortisone) with urea or salicylic acid in tropical dermatology.

Hydrocortisone acetate is the weak steroid that was selected for the WHO Essential Drugs List. It is widely used, generally available and inexpensive. It is used in various preparations. Both creams and ointments with hydrocortisone acetate have a better stability than shake lotions and are therefore the preferred formulations.

The strong steroid on the WHO Essential Drugs List is betamethasone-17-valerate. This corticosteroid is subject to degradation and must be protected from higher temperatures (see paragraph 9.5). The dilution of

commercially available strong steroid preparations is general practice throughout the world and may be cost effective (56-59). However, dilution of strong corticosteroid preparations from the Essential Drugs List often results in preparations of unpredictable stability and efficacy. We therefore discourage this practice.

4.8 Astringents

4.8.1 Introduction

Astringents have been and still are extensively used, for example in antiperspirants and deodorants, but in some pharmaceutical preparations as well. Astringent properties are useful in soothing preparations, against excessive perspiration, and for treatment of small wounds. Some astringents also have antiseptic properties.

4.8.2 Preparations

Most astringents that were once used on a large scale are now considered obsolete. Lead and bismuth salts are highly toxic after absorption and should not be used. For the same reason, soluble zinc salts should be avoided. Tannins are either almost ineffective (hamamelis) or toxic (tannic acid). The latter may be absorbed and affect liver functions.

Potassium permanganate and silver nitrate are generally used as antiseptics. They also have some useful astringent effects, but should not be used as simple astringents because they are too toxic and irritating.

The most appropriate astringent for normal use is aluminium acetate. Aluminium acetate solutions are generally stabilised with tartrate, resulting in the formation of acetotartrate. Aluminium acetate solution was previously included in the WHO Essential Drugs List but is removed. The use of aluminium acetate solution has a traditional nature, and effectiveness has not been proven. The vehicle (water) is likely to play an important role and can explain at least part of the effect. Controlled investigations comparing aluminium acetotartrate solution with the vehicle, water, have not been reported.

Aluminium acetate solution is difficult to prepare and the preparation is expensive. The temperature during preparation must remain below 30 °C. At higher temperature other, less active aluminium salts are formed.

In conclusion, we do not consider aluminium acetate solution or other astringent preparations an essential drug for reasons of doubtful therapeutic value, high costs, and difficult preparation.

4.9 Keratoplastic and keratolytic agents, moisturisers and antimitotics

4.9.1 Introduction

Hyperkeratoses, dry, scaling skin, and cell-division disorders, are clinical symptoms of many skin diseases including ichthyosis and psoriasis. The incidence of these diseases is more or less constant throughout the world and in time (60,61). Various skin diseases, including acne vulgaris, share keratinisation as common etiological factor. The different types of drugs that are used for treatment of the above skin diseases are discussed here as one group, because they generally have more than one effect. For example urea has keratoplastic, moisturising and weak antimitotic effects.

Selecting the drug of choice is difficult in this group. One should carefully consider all effects, especially the many unwanted ones, which also relate to the desired effect(s). For example, when urea is used as a moisturising agent, the skin thinning effect of keratolysis is an unwanted side effect.

4.9.2 Keratoplastic and keratolytic agents

Salicylic acid is a keratoplastic/keratolytic agent with practically no moisturising or antimitotic effects in low doses. In concentrations of 2-3% salicylic acid can dissolve the kit substance in the horny layer which is a keratoplastic effect, while in concentrations of 3% and higher it has a keratolytic effect. In concentrations of 10% and more it has a caustic effect. Due to its keratolytic effect salicylic acid enhances the penetration of corticosteroids (55). Salicylic acid has little antiseptic activity. Its usefulness in superficial infections is due to acceleration of the shedding of horny layer. This effect is more pronounced at concentrations of 5% than at 3%, which is an argument for using 5% salicylic acid in Whitfield's ointment. Acceleration of the shedding of horny layer is useful in certain acne conditions. Salicylic acid is absorbed, especially when applied on large areas of the skin or for the treatment of children. Salicylic acid is useful when a keratolytic (or keratoplastic) effect is needed and a moisturising effect is unwanted such as in mycotic infections and in acne. It is suitable in countries with a tropical climate as it is sufficiently stable; stored under dry conditions it can be kept for more than 2 years.

Salicylic acid is sometimes combined with lactic acid. Lactic acid is naturally present in skin tissue and helps to bind water to the skin. It has some moisturising effect, but the presence of a keratolytic effect is questionable. We see no place for the combination of lactic acid and salicylic acid.

Resorcinol has a keratolytic effect and some antimycotic and antipruritic effects. Absorption is possible, even through healthy skin, and systemic side effects may result for example on the thyroid gland or the development of methaemoglobinaemia. When used on the skin, resorcinol frequently causes irritation. As other drugs with less side effects are available, resorcinol should not be used.

Benzoyl peroxide has keratolytic, drying and bacteriostatic effects. In Europe it is widely used for acne. Irritation and sensitisation are major disadvantages. The drug bleaches the skin, hair and clothing. The raw material is explosive; it needs to be kept cool and moist. In Europe standardised quantities of water are added to benzoyl peroxide that is kept in stock. In hot, dry climates this water may evaporate, causing dangerous situations. Benzoyl peroxide is stronger than salicylic acid in acne but due to its physico-chemical properties it is inappropriate for tropical climates.

Retinoic acid and similar drugs accelerate both the formation and shedding of the horny layer and are useful in acne and some other skin diseases. They are used in both topical and systemic treatment. In Europe retinoic acid is mainly used in acne. The therapeutic effect in psoriasis is variable. Retinoic acid can induce serious side effects. In usual concentrations retinoic acid causes mild erythema and increases the sensitivity of the skin to ultraviolet light. Pigmentation changes may occur. After application exposure to sunlight should be avoided. Retinoic acid and similar drugs are unstable compounds. Preparations should be kept in a refrigerator and are not suitable for primary care in tropical climates. The same holds true for isotretinoin and etretinate tablets, which also cause hypersensitivity to sunlight and pigmentation changes. Additionally, they are teratogenic and pregnancy prevention is absolutely necessary. These drugs are very expensive.

Tars are keratoplastic agents with antipruritic and weak antiseptic effects. The various products are prepared from wood or coal, and are cheap. Tars are effective in psoriasis and eczema but cause a temporary

discolouration of the skin that may be cosmetically unacceptable. Phototoxicity restricts the usefulness of coal tars but not of wood tars (62,63). Tars are difficult to handle during production as active constituents (phenols) may evaporate. Tars and their volatile constituents are suspected carcinogens. Although this is still a matter of discussion, their use is discouraged in the Netherlands for this reason. Exposure to the raw materials and vapours should be avoided during preparation. Altogether, tars are a useful alternative for topical corticosteroids in psoriasis and eczema.

Sulphur has antiseborrheic, keratoplastic and keratolytic effects, and in lower concentrations may have parakeratinisation effects. It is believed that sulphur has some antiseptic effects, but this has not been validated. It has no moisturising effect. Sulphur is used in various concentrations for the treatment of acne. A 2% concentration has a keratoplastic effect and should be avoided in acne. A 3% concentration seems to be more suitable. The antiseptic effect, if it exists at all, may enhance activity in acne. In our opinion there can be a place for sulphur in primary care since it is cheap and stable, but it should be kept in mind that the activity of sulphur is still under discussion (see paragraph 4.2).

4.9.3 Moisturisers

Urea has strong moisturising properties and also has keratolytic and antimitotic effects (64). It is very useful for various dry hyperkeratotic skin diseases. Urea is used as a penetration enhancer for corticosteroids and other drugs, as discussed in paragraph 4.7 (54). Urea is used in dry skin conditions for example in ichthyosis, but epidermal thinning is a serious side effect to consider, especially with long-term use. Urea is well tolerated but stings in higher concentration. It is moderately stable, and can be used if certain precautions are taken (see paragraph 9.8).

Urea is sometimes used in combination with lactic acid. Lactic acid is naturally present in the skin where it plays a role in water binding. It is widely used as a moisturiser and has shown to be effective (65), although literature to substantiate this remains scarce. Lactic acid is well known as a common ingredient in cosmetics and side effects are rare.

Sodium chloride (household salt) has a moisturising effect on the human skin. It has no keratolytic or antimitotic effects (66). It is seldom used in dermatology but some dermatologists use it for dry skin with satisfactory results. As it is readily available throughout the world and is cheap, it could have been a good choice for primary health care provided more information were available. To our knowledge controlled trials are lacking and the use of sodium chloride thus cannot be recommended.

Petrolatum and other occlusive arrangements, such as plastic wrappings, have strong moisturising effects with no antimitotic or keratolytic side effects. Petrolatum is relatively stable (see paragraph 5.2); physical instability is relatively unimportant when it is used as pure substance. Petrolatum does not cause epidermal thinning, but folliculitis may develop especially when used on the legs.

4.9.4 Management of dry skin in leprosy

Leprosy patients often suffer from loss of normal sweat secretion secondary to nerve destruction. This leads to a dry skin. Dry skin is prone to develop surface cracks in the dehydrated keratin layer. Infection, inflammation and ulceration may develop from such cracks especially on the palm of the hand and the sole of the foot. Additionally, dry skin looks bad and is slippery. It is therefore important that leprosy patients keep their skin hydrated (32).

Normal sweat secretion is not present in leprosy patients. Therefore, water has to be supplied from the outside by soaking the affected skin in a water bath for 10 to 20 minutes once daily. After hydration of the skin, and excess water has been wiped off and petrolatum or some other oil has to be applied to keep the water in. This daily procedure has been taught by generations of leprosy workers and is found in many booklets on the treatment of leprosy (32,34). A study referred to by Brand and Fritschi (32) indicates that the daily soaking procedure is not absolutely necessary provided the petrolatum or oil is applied regularly. Nevertheless, we suggest to keep using the old experience-based methods.

An occlusive, inert barrier at the lowest price is preferred to keep the skin of leprosy patients hydrated. For this purpose we recommend petrolatum. It is cheap and causes few side effects, apart from the adverse effects of occlusion itself. A side effect of petrolatum is folliculitis that develops especially on the legs (11). Locally produced vegetable oils are an excellent choice too, provided they are not sensitising. Another alternative is emulsifying ointment but it is far more expensive than plain petrolatum. Expensive moisturisers such as urea cream have no advantages for this indication over the soaking and occlusion procedures described above.

4.9.5 Antimitotics

Dithranol is widely used for the treatment of psoriasis. The prevalence of psoriasis in Europe and East Africa is about 2%, whereas in West Africa a lower prevalence has been reported. Dithranol disrupts mitochondrial function and structure, thereby affecting the energy metabolism of the cell. White skin seems to be somewhat more sensitive to dithranol than black or coloured skin. Dithranol is highly active and should be used on diseased skin only. Care should be taken to avoid contact of dithranol with healthy skin. The solubility of dithranol in paraffins is only 0.25% and it is practically insoluble in water. Dissolution is even more limited in preparations containing lower amounts of paraffins, such as lanette cream (35% paraffins, 0.1% dissolution) or zinc paste (50% paraffins, 0.13% dissolution). Preparations with more dithranol have a longer action because of a depot function. The disadvantage of depot preparations is the risk of spreading the excess dithranol onto healthy skin adjacent to the treated parts. Zinc paste is a relatively stiff preparation, and spreading is likely to be limited. Pastes are less occlusive than ointments, and the solubility of dithranol is less in such a formulation. Thus, limited activity can be expected, but has not been documented. Creams are less occlusive than pastes, and the solubility of dithranol is poor. Creams are expected to be the least active preparations, which indeed has been reported in the literature (67-69). On the other hand, an advantage of dithranol cream is that it can be rubbed into the skin and the spreading of excess dithranol to healthy parts of skin will be less (68). Dithranol can be dispensed in petrolatum or emulsifying ointment (both are occlusive and most effective), zinc paste together with 2% salicylic acid (less occlusive and less spreading), or lanette cream after addition of 0.5% ascorbic acid (less occlusive, no spreading but also less effective). Dithranol is unstable and should not be used in primary care treatment. Patients with severe psoriasis requiring dithranol treatment should be treated in a hospital.

Podophyllum resin is an extremely toxic agent. It can be used as a caustic on serious warts and condylomata. When condylomata are highly prevalent regionally, there can be a place for this drug but not in primary care.

4.9.6 Conclusions

In primary care treatment there is a place for salicylic acid (alcoholic solution) or sulphur (shake lotion) when keratolytic and drying effects are required for example in acne, and for urea cream when keratolytic and moisturising effects are required for example in ichthyosis. Both salicylic acid and urea are included in the WHO Essential Drugs List.

Dithranol, podophyllum, fluorouracil and tretinoin are used in hospitals for various diseases when other drugs are ineffective, but are unsuitable for primary care treatment.

Coal tar is included in the WHO Essential Drugs List. There is a place for such preparations, but phototoxicity restricts its usefulness in tropical countries.

Petrolatum or locally produced vegetable oil can be included in the formulary for skin care of leprosy patients in regions where the disease is prevalent.

4.10 Antipruritics

4.10.1 Introduction

Itch is a symptom of many skin diseases and of some systemic diseases as well (e.g., scabies, diabetes, uraemia, Hodgkin's disease). Before treating any serious itch the underlying cause needs to be established and treated adequately. Treatment of the itch itself may be indicated. For example in scabies itch may continue for weeks after all the mites were killed and continuous scratching may lead to secondary infections. Treatment of itch is a sensible preventive measure in such circumstances.

4.10.2 Vehicle and active ingredients

The choice of the vehicle is very important for the treatment of itch. Cooling the skin for example by just applying cold water, promotes itch relief and such effects can be substantial. Many drugs are available for the treatment of pruritus but most of them are unsuitable. They are mentioned briefly.

Corticosteroids have direct and indirect antipruritic effects. Symptomatic relief of underlying diseases can also play a role. Corticosteroids may cause some serious side effects like atrophy of the skin. They should not be used when safer drugs are effective. Long-term treatment of corticosteroids should be avoided.

Antihistamines were widely used on the skin for insect bites. They have a high (photo)sensitising potential. In countries and climates with a lot of sunshine, photosensitisation is an important issue and these drugs should not be applied on the skin.

Local anaesthetics are effective in certain specific cases. Some products such as benzocaine are sensitising. Lignocaine (which is called lidocaine in some countries) and pramocaine (pramoxine) are suitable for use on the skin, but may be ineffective.

Menthol and camphor have some anaesthising effect in low concentrations but have stimulating effects in concentrations of 0.25% to 1% which are generally used for antipruritic treatment. The stimulating effect on nerves in the skin changes the perception of itch. Menthol may cause contact dermatitis. Both menthol and camphor are absorbed even through healthy skin. In infants these agents may cause laryngospasms with fatal outcome even after topical treatment. Therefore menthol and camphor should never be used in small children.

Calmitol, a branded product, contains chloral hydrate, camphor, iodated oil, menthol, hyoscyamine, chloroform, ether and zinc oxide. Such combination preparations should not be used.

Phenol has anaesthetic, antipruritic and antiseptic properties. In a concentration of 0.5% to 1% phenol has antipruritic properties. For antiseptic effects concentrations up to 2% are used. Phenol in concentrations higher than 2% is used for example as an anaesthetic for post herpetic pain (5%) or as a caustic agent. Phenol causes various side effects. Local irritation and necrosis may occur, but sensitisation is uncommon. Pigmentation disorders may occur. All reports on local side effects concerned concentrations of 1% or more. Phenol is absorbed through the skin. Absorption through inhalation after topical application is possible. Local use of 0.5% seems to be reasonably safe. Precautions should be taken in the preparation of phenol containing drugs as the pure compound is caustic and toxic. Phenol has a limited shelf life (see paragraph 9.6).

In making a choice for antipruritic treatment, both the vehicle and the active ingredient need careful consideration. Shake lotions are most effective. The high pH of such preparations makes preservation often difficult but calamine lotion offers a good formulation. It contains 0.5% phenol and is considered the best choice as the preparation is both active and stable at higher temperatures (see paragraph 5.5). Side effects of phenol are likely to be mild when 0.5% is used. Calamine lotion is also included on the WHO Essential Drugs List as antipruritic preparation. Local anaesthetics can be used, but are more expensive and may only be effective in specific situations.

4.11 "Indifferent" vehicles

4.11.1 Introduction

In dermatological treatment the effect of the vehicle is substantial. This is not considered a placebo effect but is the result of applying various ingredients to the skin. Vehicles may be soothing, occlusive, cooling or protecting. Vehicles therefore are never indifferent.

4.11.2 Vehicles

Although the "indifferent" vehicles contain no active drug ingredient, they may still cause various side effects. Sensitisation and irritation are frequently seen, for instance in response to preservatives and wool alcohols. Some vehicles are useful in primary dermatological care.

Calamine lotion (see paragraph 4.10) contains phenol as a preservative and antipruritic agent. Calamine lotion has general soothing, drying and antiseptic properties. Zinc may promote healing but is also toxic when large quantities are absorbed (70,71). Thus, the lotion should not be used on large wounds as zinc may dissolve and be absorbed. Calamine lotion is stable under tropical conditions (see paragraph 9.6.2). The formula can be adapted (see paragraph 5.5) to obtain equally effective but cheaper preparations.

Zinc paste is a vehicle with protective properties. It permits some water to pass through, and is therefore not as occlusive as petrolatum. The risk of absorption of zinc is minimal when zinc paste is used on wounds, because the zinc oxide particles will not contact fluids. Zinc paste is an effective physical sunscreen (see paragraph 4.12). The formulation of zinc paste needs adaptation when it is produced and used in tropical conditions (see paragraph 5.3).

Petrolatum is used for its occlusive or protective properties. It is also used as a hydrating agent (see paragraph 4.9).

Clean water is used in various skin diseases. Evaporation on the skin has a cooling and drying effect. It is used as hot or cold compresses.

4.12 Sunscreens

4.12.1 Introduction

Exposure to sunlight may cause acute and chronic skin damage. DNA damage may cause skin cancer. Our skin has mechanisms to protect itself from this type of damage. Adaptive mechanisms of the skin include epidermal thickening and pigmentation. Pigmented skin is less sensitive to sunburn than white skin.

In some people the natural defence mechanisms of the skin are not present or insufficient for example in albinism. In other cases such as photosensitivity or systemic lupus erythematosus there is extreme sensitivity to sunlight. All these cases require adequate protection against sunlight for which regular sunscreens are insufficient. A number of studies have shown that adequate sun protection is often lacking for example in albinism (72,73).

The best advice for these people is to stay indoors to avoid any direct sunlight at times protection is absolutely required. Tightly knitted and dry clothing provides adequate protection (74). In contrast, loosely knitted or wet clothing may permit some radiation to pass. A wide brimmed hat is also advisable (75). Sunscreens are another option but they are expensive and only partially effective. Albinos also need to wear sunglasses because their retinas are sensitive to sunlight as well.

4.12.2 Sunscreen ingredients

Sunscreen agents are divided into physical and chemical sunscreens. Physical sunscreens contain high amounts of powders that scatter sunrays thereby preventing radiation from reaching the skin. Zinc paste is an example of a physical sunscreen but from a cosmetic point of view it is usually unacceptable.

Chemical sunscreen agents absorb specific parts of the radiation thereby providing partially effective protection. Most chemical sunscreens have their peak absorption in the mid-range ultra violet spectrum (UVB; 290-320 nm). UVB only penetrates the outer layer of the skin and causes sunburn. UVA (320-400 nm), and especially UVA1 sunlight (340-400 nm) penetrates the skin much deeper and is responsible for skin tissue damage. It also causes tanning. Photosensitivity reactions are often caused by UVA. For a chemical sunscreen to be effective it must absorb UV radiation over a wide range. Most importantly it should absorb radiation in the UVA range, and preferable in the UVA1 range. As single sunscreens will never have such a wide range of protection they are often used in combinations, but these are more expensive (76,77) .

Chemical sunscreens are characterised by a number of parameters. The sun protection factor indicates how much longer the skin can be exposed to sunlight before sunburn occurs. The sun protection factor of a sunscreen is difficult to determine, because it is dependent on the vehicle in which it is processed and the type of skin it is applied to. Another parameter is the substantivity which indicates the tendency of the sunscreen to remain on the skin after sweating, bathing and swimming. Lastly, the protection range, for which the term “broad spectrum” is used, indicates whether the sunscreen protects against UVA (76).

Most of the chemical sunscreens can cause (photo)sensitivity reactions themselves. Many may also cause irritation. Sunscreens are often used for longer periods or even a life time especially in tropical climates and conditions like albinism. Long-term safety is thus very important.

A suitable and simple sunscreen was developed by the Netherlands-based African Albino Foundation (78). It contains octinoxate 8%, a chemical broad spectrum UV absorbant, and titanium dioxide 10%, a physical sunscreen, in petrolatum. This mixture has a high sun protection factor of at least 20 and due to the petrolatum vehicle also a high substantivity. Octinoxate, which is chemically a cinnamate ester, is one of the most frequently used chemical UV absorbers and as a result its risks are well known. Some safety concerns were raised following a study that demonstrated toxicity to mouse cells at concentrations readily reached after topical use (79). In contrast, a more recent study concluded that octinoxate does not sufficiently penetrate the outer skin to cause any relevant toxicity (80). There is also concern about an estrogenic effect of octinoxate during pregnancy and harmful effects were shown in animal testing in rats (81). Whether such effects also occur with other sunscreen agents is still unclear. To be safe, our advice is against the use of octinoxate and similar sunscreens during pregnancy. Zinc paste is an alternative during pregnancy. There are safety concerns about the use of titanium dioxide as nanoparticles but these are of no relevance for the preparation in this formulary as it contains "regular size" titanium dioxide.

References

As a useful and practical introduction to skin diseases in Africa we recommend the book *Common skin diseases in Africa, an illustrated guide* by Van Hees and Naafs, which is freely available from TALC UK (82). The *ABC of Dermatology* by Buxton provides more detailed information on skin diseases and their management (83).

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5 Dermatological vehicles suitable for the tropics

This chapter focusses on the pharmaceutical and technological issues that are relevant to the dermatological preparations in this formulary. Our focus is on preparations that are easy to prepare and use and are suitable for tropical climate conditions. The preparatory considerations and choices aim to meet these criteria. The chapter opens with a general introduction on dermatological preparations and continues with some specific issues relevant to the formulary.

5.1 Introduction to dermatological preparations

5.1.1 Types of dermatological preparations

Dermatological preparations vary by their physical form and consistency. We distinguish the following forms:

- Solid preparations: powders
- Semi-solid forms: ointments, gels, pastes, creams
- Liquid forms: solutions, suspensions (e.g., shake lotions), thin emulsions

The semi-solid and liquid preparations are the most important and frequently applied forms on the skin. Ointments are defined as one phase in which solid or liquid substances are dispersed. We distinguish hydrophobic ointments, water emulsifying ointments and hydrophilic ointments. Hydrophobic ointments are fatty preparations that only absorb minor quantities of water. Water emulsifying ointments are fatty preparations as well. Due to the presence of emulsifiers (detergents) they absorb more water to form a water-in-oil, or an oil-in-water emulsion. Hydrophilic ointments have a fatty appearance but are miscible with water. Creams consist of a lipophilic and a hydrophilic phase combined with one or more emulsifiers. In hydrophilic creams the outer phase is aqueous, whereas in lipophilic creams the outer phase is fatty.

5.1.2 Constituents of dermatological preparations

Dermatological preparations may contain three different phases: a fat, a liquid and a solid phase. Table 5.1 lists the constituents that are used in these phases and a brief description of their chemistry and main properties.

Table 5.1. Constituents often used in the fat, liquid and solid phase of dermatological preparations

Phase	*Chemistry*	*Examples*	*Main properties*
Constituents of the apolar fat phase			
Waxes	*Esters: fatty acids + fat alcohol*	*Beeswax, wool fat*	*Change consistency, sometimes emulsifying*
Fatty oils and fats	*Esters: triglycerides*	*Plant-derived oils*	*Change consistency, penetration enhancement, solvent for lipophilic compounds*
Mineral oils	*Saturated hydrocarbons*	*Petrolatum, paraffin*	*Change consistency, occlusion*
Fat alcohols	*Alcohols with long hydrocarbon chains*	*Cetylalcohol, cetostearyl alcohol*	*Emulsifiers (w/o)*
Lipophilic excipients	*Various*	*Antioxidants*	
Lipophilic drugs (dissolved)	*Various*	*Often phenolic compounds or corticosteroids*	*Therapeutic effects*
Constituents of the polar liquid phase			
Volatile solvents		*Water*	*Solvent, drying, cooling*
		Ethanol	*Solvent, strong drying, strong cooling, preservative (≥15%), disinfectant*
Non-volatile solvents		*Propylene glycol*	*Solvent, preservative (≥15%), humectant*
		Glycerol	*Solvent, preservative (≥30%), humectant*
Dissolved excipients		*Viscosity enhancers Antioxidants Preservatives*	
Hydrophilic drugs (dissolved)		*Various*	*Therapeutic effects*
Constituents of the solid phase			
Zinc oxide	*ZnO*		*Enhancement of consistency, drying, enhancement of cooling effect, covering, slightly astringent*
Talc	*Magnesium silicate with some aluminium silicate*		*Enhancement of consistency, drying, covering, protecting*
Starch	*Polysaccharides: amylose, amylopectin*		*Enhancement of consistency, strongly drying, covering*
Drugs (dispersed)		*Various*	*Therapeutic effects*

Antioxidants are used to ensure the quality of dermatological preparations and to prolong their shelf and storage life. The standard redox potential of the antioxidant (in its reduced form) is lower than the standard redox potential of the substance requiring protection (the drug). In the presence of oxygen the antioxidant is oxidised and not the drug. An antioxidant is added in an excessive amount for long protection. Antioxidants are fat or water soluble. Examples of fat-soluble antioxidants are dl-α-tocopherol (vitamin E)

and butylhydroxytoluene; examples of water-soluble antioxidants are ascorbic acid (vitamin C) and sodium pyrosulphite.

Many dermatological preparations also contain preservatives for quality enhancement because the water phase is sensitive to microbial contamination and decay. Sterilisation of dermatological preparations is uncommon unless they are used on open wounds. The addition of preservatives prevents the growth of micro-organisms. Frequently used preservatives in dermatological preparations are sorbic acid and parahydroxybenzoic acid derivatives (parabenes).

The quality of the water for dermatological preparations is of great relevance. Micro-organisms in the water are killed by cooking it shortly before use. This results in an initially low level of contamination of the product. Additionally, regular water contains minerals that are incompatible with other ingredients, especially ionogenic emulsifiers. The preparations included in the formulary are sufficiently robust to be prepared with safe drinking water. More information on safe water is found in the appendix.

Water and oil or fat are immiscible, but they are major constituents of dermatological preparations. Adding emulsifying agents allows stable systems containing water and oil or fat to be formed. Emulsifiers are distinguished as producing oil-in-water (o/w) or water-in-oil (w/o) systems. Also, they are classified as ionogenic or non-ionogenic (see table 5.2).

Table 5.2. Emulsifiers used in dermatological preparations

Type	***Example***	***System***
Ionogenic	*Alkyl sulphates*	*o/w*
	Quaternary ammonium salts	*o/w*
Non-ionogenic	*Polyethylene glycol fat alcohol ethers (cetomacrogol)*	*o/w*
	Sorbitan oleate (Span 80)	*w/o*
	Polyethylene glycol sorbitan ethers (polysorbate 80, also known as Tween 80)	*o/w*

Alkyl sulphates are incompatible with large anions, and quaternary ammonium salts with large cations. Cetomacrogol is incompatible with phenols in concentrations higher than 2%.

Viscosity enhancers are used to prepare hydrogels. Cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose), inorganic colloids (colloidal aluminium magnesium silicate), polyacrylic acid derivatives (carbomers) are used, as well as products of natural origin (e.g., tragacanth). Table 5.3 lists the typical composition of various dermatological preparations.

Table 5.3. Typical composition of dermatological preparations

Dermatological preparation	***Constituents***
Hydrophilic cream	*Fatty oil, fat or wax, o/w emulsifier, humectant, preservative, water*
Hydrophobic cream	*Fatty oil or fat, wax (sometimes), w/o emulsifier, water*
Hydrogel	*Viscosity enhancer, humectant, preservative, water*

5.2 Ointments

5.2.1 Introduction

Ointments are semisolid fatty preparations in which solids or liquids are dispersed. The types of ointments generally used in dermatology are:

- Hydrophobic ointments: absorb only very small amounts of water.
- Emulsifying ointments: absorb larger amounts of water thereby forming an oil-in-water cream.
- Hydrophilic ointments: completely water miscible.

Fatty creams of the water-in-oil type are sometimes also classified as ointment.

The therapeutical properties of an ointment depend on the various oils and fats it contains:

- Paraffins produce non-washable ointments that do not penetrate the skin. Drugs in such ointments exert only superficial activity. Paraffins are occlusive.
- Paraffins combined with water-in-oil emulsifiers produce ointments that are slightly more penetrating and less occlusive. Small quantities of water are absorbed by these ointments but they are still difficult to wash away.
- Paraffins and oil-in-water emulsifiers form emulsifying ointment type vehicles. They are washable and suitable for hairy skin, not very occlusive and often allow penetration of active ingredients incorporated in them. Adding water results in vanishing creams of the oil-in-water type.

Using oils and waxes instead of paraffins results in more penetrating preparations.

5.2.2 Oleogels

Oleogels are semisolid preparations consisting of a liquid and a gel forming agent. The gel forming agents form stable three dimensional structures that bind the liquid phase. Such structures are produced when gel forming particles form secondary bindings with each other (van der Waalsbindings, H-bridges). These particles are unable to migrate through the liquid phase.

Oleogels are often thermo reversible but not always. Upon heating the three dimensional network breaks down into a liquid. Upon cooling the three dimensional structure is often formed again but sometimes the gel forming agent fails to re-establish the network. Breakdown of the oleogel structure, and thus liquidification of the gel, also occurs under other circumstances, for example when the gel is stirred vigorously. Formation of the oleogel structure takes time. Some gels harden during the weeks following their preparation due to further formation of the network structure. As the gel network tightens, some of the liquid phase is pressed out. This is called bleeding or syneresis.

The stability of an oleogel mainly depends on the:

- Form of the particles of the solid phase.
- Physicochemical properties of the solid phase and its ability to form secondary bindings.
- Concentration of the solid phase.
- Physicochemical properties of the liquid phase.

5.2.3 Petrolatum

Petrolatum (soft paraffin, vaseline) is an oleogel. Its properties change with origin and supplier. Petrolatum consists of solid branched alkanes that form a gel structure in liquid unbranched alkanes. The structure of the gel is characterised by so called "fransenmicellen". In this system the branched solid ***iso***-alkanes have the best gel forming activity and unbranched solid ***n***-alkanes are responsible for a thicker

consistency. The ***i/n*** ratio of the solid phase and the solid/liquid ratio of the petrolatum determine the characteristics of the resulting gel (1-3). Upon heating the solid alkanes melt and form a homogeneous melt. At intermediate temperatures (35 to 45 °C) some of the solid alkanes melt while others are still in the solid phase. This results in a smaller amount of the solid gel forming phase and a larger amount of liquid phase. This partial melting of the oleogel looks like bleeding but it is a different phenomenon. It causes separation and due to this relative instability of the oleogel, petrolatum containing preparations always require mixing before dispensing or use.

5.2.4 Ceresin

Petrolatum gels are stabilised by changing the content of higher melting alkanes in the solid phase. The addition of microcrystalline wax or ceresin has this effect; the latter is the most appropriate because it has a favourable i/n ratio (1). However, in our experiments the addition of ceresin failed to produce an ointment base that was stable at temperatures up to 45 °C (unpublished results). This was not unexpected, since the solid/liquid and i/n ratios only have slight effects on the melting characteristics of the ointment and on bleeding. A little less oil is pressed out, compared to pure petrolatum, but the change is insufficient to solve the instability problem (3).

5.2.5 Cetostearyl alcohol

Another way to stabilise petrolatum gels is the addition of another gel forming system. This solution was chosen in the *British Pharmacopoeia* recipe for emulsifying ointment and some other ointments. Various emulsifiers are used for this purpose such as cetostearyl alcohol, spans and glyceryl monostearate (4,5). These emulsifiers form a second, independent gel system.

Cetostearyl alcohol exists in various (liquid) crystalline states. This is called polymorphism. Upon heating at 38 °C the pure cetostearyl alcohol changes from the β-modification into the α-modification. The latter melts at 51 °C. In the α-modification the hydrophobic parts are more orderly arranged (parallel) than in the β-modification. Upon cooling, this molten cetostearyl alcohol solidifies into the α-modification at 48 °C and slowly rearranges again into the β-modification below 23 °C (6).

Cetostearyl alcohol forms a gel system in paraffins (including petrolatum) in both the α- and the β-modification. The β-modification is expected to give a better gel forming system than the parallel arranged α-modification. The effect of the second gel forming system adds to the effect of temperature on the petrolatum gel (see paragraph 5.2.3). When the ointment is prepared by melting, it requires storage below 25 °C for some time to allow a stable gel to be formed. This explains the recommended maximum storage temperature of 25 °C for emulsifying ointment in the *British Pharmacopoeia* (7).

5.2.6 Other gel forming emulsifiers

The polymorphic properties of cetostearyl alcohol are caused by the presence of a fatty alcohol chain in the molecule. Other emulsifiers that are suitable for ointments share the same characteristics. Pure fatty alcohols with an even number of C atoms prefer the β-modification, those with an uneven number the α-modification, while mixtures tend to prefer the α-modification (8). The pure fatty alcohols with an even number of C atoms are likely to give the best results in stabilising petrolatum gels. Regular pharmaceutical qualities of stearyl alcohol, however, contain enough by-products to allow the α-modification to exist at low temperatures (9). Using other stabilisers may change the temperatures at which polymorphic changes occur, but they are in the same range as described. Hence, the addition of

such stabilisers does not solve the instability problem of petrolatum. All systems we tested were partially melted and inhomogeneous at 45 °C (unpublished results).

5.2.7 Water and cetostearyl alcohol

Adding water to gel systems containing cetostearyl alcohol further complicates the picture. In such a system one more phase exists, i.e., the hydrophilic liquid phase. The system contains a water/fat interface. Cetostearyl alcohol has both a hydrophilic and a hydrophobic side, and prefers the interface layer. The hydrophilic side is small and the hydrophobic side large. The α-modification with its parallel arranged hydrophobic sides is more suitable to occupy the interface, and hence is more stable (10). The same holds for binary systems of cetostearyl alcohol and water. The stabilisation of the α-modification in the presence of water has been reported in the literature (11). Due to the parallel arranged hydrophilic sides the α-modification fits better at the interface and forms a more stable oil/water layer than the β-modification. Thus, co-emulsifiers in the α-modification tend to give better results in creams (9).

The gel structure in water containing ointments is expected to be more stable and exist over a wider temperature range than in ointments without water. Despite this, more separation of oil may occur because the α-modification is a less effective gel forming agent. This was observed in practice (unpublished results). In creams with an oil-in-water structure the same effect is observed but in this case separation of oil is impossible because every oil particle is surrounded by water.

5.2.8 Plastibase

Plastibase is an ointment base containing 5% polyethylene 21,000 as gelling agent in liquid paraffin. The quality of the polyethylene is important. The gel is formed only under very specific cooling conditions (12). The mixture should be melted at 130 °C and quickly cooled by pouring it over cold steel plates that are kept at a temperature below 50 °C. If these conditions are not met a useless mixture of crystalline polyethylene and paraffin results (13,14).

The consistency of plastibase is fairly constant between -15 and 60 °C. Molten plastibase does not form a gel again upon cooling, unless the specific conditions described above are met. In practice, it is highly unlikely that the gel is formed again after melting. As in tropical countries temperatures of 60 °C and higher are expected for example during transport plastibase is an unsuitable ointment base for the tropics.

5.2.9 Inorganic gelling agents

It is possible to obtain stable gels by using inorganic gelling agents in petrolatum or oils. This principle is also applied in suppository technology (15) and may be an option for dermatological preparations. Aerosil gels in petrolatum showed excellent thermo stability at 70 °C (unpublished results). However, these gels are not widely accepted in dermatology because they cause a very unpleasant feeling on the skin.

5.2.10 Other fatty ointment bases

Various other ointment bases are used in dermatology. Lanoline/petrolatum bases were, and still are, widely used. Lanoline bases are generally less stable than petrolatum (4). Lanoline (or wool fat) derivatives may cause allergic contact dermatitis and are better avoided (16,17). The allergic reaction is probably caused by alcohols in lanoline. Therefore, taking only the alcohol fraction as in wool alcohol

ointments does not solve the problem (16). Beeswax or similar agents were inappropriate gelling agents as they form unstable ointment bases (unpublished results).

5.2.11 Microbial problems with fatty ointments?

All dermatological preparations are prone to contamination with micro-organisms during use. Micro-organisms need water and nutrients to survive. Since there is no water, fatty ointments will not promote bacterial growth. Some micro-organisms however, especially spore-forming bacteria, are able to survive. Years after contamination bacteria, even non-spore forming species, were detected in both vegetable and mineral oils (18). Infection transmission from an ointment that was contaminated during use or preparation is therefore possible.

5.2.12 Conclusions

Ointments generally become inhomogeneous at temperatures that are no exception in tropical countries. There are no preparations without the likelihood of getting inhomogeneous during storage in tropical climates. Therefore some precautions are essential for using ointments in tropical conditions: before dispensing the ointment to the patient, and before it is applied to the skin, the ointment needs to be stirred or mixed to re-homogenise it again.

Plastibase does not provide an alternative for ointments. Its properties are better than those of petrolatum, but still not optimal. Once molten, it can no longer be used. It is also difficult to obtain and expensive. Local production of plastibase is not feasible.

Emulsifying ointment is the most appropriate general ointment base for tropical dermatology because it is washable (and hence suitable for hairy parts of the skin) and relatively non-occlusive. Petrolatum is an alternative but cannot be washed away from the skin and is occlusive. Petrolatum with 10% wool fat can be used, but has the same disadvantages. In addition, wool fat has sensitising properties. Water-in-oil creams are less stable and prone to microbial contamination and are not considered appropriate.

5.3 Pastes

5.3.1 Introduction

Pastes contain large amounts of solid phase in a liquid or semi-solid base which is either lipophilic (fatty) or hydrophilic (aqueous). Pastes are soft, semisolid preparations. Calamine lotion is not considered a paste although it contains approx. 23% solid matter.

Pastes are disperse systems. Their properties depend on the type and concentration of the solid phase, and the type of liquid or semisolid phase. Pastes that contain water as liquid phase are microbiologically vulnerable and may separate. Liquid preparations such as calamine lotion are preferred, because they are easily rehomogenised.

The pastes included in this formulary are hydrophobic pastes. Due to the high powder contents they are not occlusive; some can even absorb fluids and have drying properties. Pastes are used as protecting agents (e.g., against sunburn) or as soothing agents. Most pastes do not melt on the skin and they do not promote penetration of the active ingredients. They are only suitable as vehicles for drugs that are active on the skin

surface. Pastes are difficult to wash off because they do not contain an emulsifying agent and should therefore not be used on hairy skin. The best way to remove pastes is to rinse the skin with some vegetable oil.

Various powder ingredients are used in pastes. Zinc oxide and starch are amongst the most widely used. Starch has major disadvantages for use in hot and humid climates because it is microbiologically unstable (19). The absorption of zinc after dissolution in wound exudates has been described but is probably not clinically relevant when using pastes (20).

Petrolatum and vegetable oils are often used as lipids in pastes. Pastes with petrolatum are less soothing and less penetrating than those with vegetable oils, and are used for fixation of drugs on the skin (e.g., dithranol) and as a protective.

5.3.2 Zinc paste

Many pharmacopoeias include zinc paste or similar preparations. They usually contain 25% zinc oxide, 25% starch and 50% paraffins. These pastes have protecting properties but are not occlusive due to the high powder content. The pastes are rather stiff. They are used to fix drugs on the skin. These pastes showed physical stability at 45 °C and 70 °C (unpublished results).

Emulsifiers can be added to a paste. It makes the paste washable and suitable for hairy skin. Unfortunately, such pastes with emulsifier showed physical instability at 40 °C and 45 °C (unpublished results) and hence are less suitable for the tropics. Pastes with an emulsifier have other therapeutical properties than those without. The presence of an emulsifier enhances the penetrating effect, which adds to the effect of the melting on the skin.

Zinc pastes usually contain 50% powder phase. Pastes with less powder have other characteristics and hence are suitable for other indications. However, they are physically unstable at 45 °C. Pastes with less than 50% powder are therefore inappropriate for tropical climates.

Pastes usually contain starch. Starch is thought to enhance the paste's capacity to absorb water. We tried to demonstrate the uptake of water in a paste containing 25% starch by treating it with iodine solution to induce the typical blue colour of iodine bonded with starch. We did not observe any change of colour (unpublished results) and concluded that the water absorbing capacity of starch in pastes seems unlikely, maybe due to a lack of contact between the starch particles and passing fluids. We concluded that the therapeutic effect of a paste is due to the high powder content and not to the absorption of water by specific ingredients.

Starch is widely available throughout the world but it has some serious disadvantages for pharmaceutical use. Starch is generally contaminated with various micro-organisms. During storage at higher relative humidity the raw material absorbs water and may become wet enough to allow microbial growth (19). Using such starch produces contaminated pastes. Therefore starch is better avoided in pastes. Instead of using 25% starch and 25% zinc oxide, we prefer to use 50% zinc oxide as the powder phase of zinc paste.

Western pharmacopoeias sometimes prescribe the addition of some liquid paraffin to improve the spreadability of the paste. This is not necessary and can be left out.

We conclude that pastes are suitable for use in tropical climates. A good and simple formula is zinc oxide 50% with petrolatum 50%.

5.3.3 Zinc oil

Zinc oil contains zinc oxide (usually 60%) and vegetable oil. This is a (semi)liquid preparation with soothing and drying properties. Most oils are appropriate provided they have a low sensitisation potential. Sesame oil for example has a high sensitisation potential and should be avoided in dermatology.

The acid value of an oil indicates the amount of free fatty acids. An oil with a rather low acid value should be chosen to prepare zinc oil, because zinc oxide reacts with the acids. This results in a stiffer preparation with reduced stability. Oils with an acid value of 12 or less are suitable (unpublished results). Since current vegetable oils generally have lower acid values, there is no need to specify the oil in the recipe.

Zinc oil should not be packed in plastic containers as "corrosion" of the plastic material may occur. It should be stirred or mixed before dispensing or use. The packaging should allow this.

5.3.4 Preparation techniques

For a homogeneous paste or oil preparation the zinc oxide requires passing through a sieve before mixing with the petrolatum or oil. An alternative method is to thoroughly mix small quantities of zinc oxide with small quantities of petrolatum or oil at a time. This produces reasonably homogeneous pastes (unpublished results) when for example sieves are unavailable.

5.4 Creams

5.4.1 Introduction

Creams contain at least one hydrophilic constituent, which is generally water, one lipophilic constituent, and an emulsifier. Classical creams are disperse systems in which either the lipid is dispersed in the water phase (oil-in-water, o/w) or the water in the lipid phase (water-in-oil, w/o). The inner phase consists of small droplets that have some mobility. A third class is that of ambiphilic creams. These consist of two continuous phases and it is no longer possible to distinguish an outer and an inner phase (21).

Water-in-oil creams are inappropriate for use in tropical conditions as they are physically unstable (see paragraph 5.2.7). Ambiphilic creams have a rather fatty consistency but are relatively non-occlusive. They are more appropriate than oil-in-water creams especially for unstable drugs, such as strong corticosteroids (21,22). However, ambiphilic creams require more expensive raw materials and their physical stability at extreme temperatures is not well known. Therefore we decided to use the more classic oil-in-water cream type in this formulary.

The water in an oil-in-water cream starts to evaporate upon application on the skin. This has a slight cooling effect. The creams are also called vanishing creams, referring to the thin oily layer that remains on the skin. This has little occlusive effect and may even have a drying effect. Many drugs can be dispensed in creams, although incompatibilities are not uncommon and should be taken into account.

5.4.2 The cream system

The physical instability of a cream is caused by two mechanisms, creaming and coalescence.

Creaming is caused by the differences in relative densities between the oil and water phases, causing the lighter phase to float on the heavier one.

Coalescence is the union of small droplets to form bigger ones, which ultimately leads to complete separation of the oil and water phases. In a vanishing cream the oil phase is dispersed in the water phase. The oil forms small droplets. The smaller the droplets, the larger their relative surface area, and the larger the interface between the oil and water phases is. This situation is energetically unfavourable. The system will strive for the most favourable situation, thus the smallest interface, thus the largest droplets, thus complete separation. Hence all emulsions are unstable and tend to separate.

Creams need stabilisation to avoid separation. There are two ways of doing this. The first is preventing contact between droplets by using thickening agents, the second is preventing coalescence of droplets by using emulsifiers. Emulsifiers are the most widely used stabilisers. An emulsifier has a hydrophilic part and a lipophilic part. The first wants to dissolve in water, the second in oil. Thus the emulsifier will accumulate at the oil/water interface. This is energetically a very favourable situation. The hydrophilic part of the emulsifier resists being pulled into the oil phase, the other part resists being pulled into the water phase.

Various gel phases can also be added to a cream. Most creams are therefore very complex systems. The properties of a cream depend on the type and proportion of water and oil phases and emulsifier, and preparation techniques. These topics are dealt with in the following paragraphs.

5.4.3 The oil phase

Various fats and oils are used in creams, for example petrolatum, vegetable or synthetic oils, and waxes. The latter are widely used because the resulting creams are less greasy, more penetrating and hence cosmetically more acceptable. Cetiol V (oleyl oleate) is the most extensively used wax.

Waxes have some major disadvantages, such as being more expensive, more difficult to obtain, less stable and being better solvents. An unwanted effect of their high solvent power is that waxes may inactivate preservatives. Drug penetration is enhanced due to better penetration of the oil phase, or diminished due to greater affinity of the drug with the vehicle (23,24). The overall effects also depend on the properties of the drug. The final outcome is therefore difficult to predict on the constituents of the cream base alone.

Vegetable oils have an important advantage: in many countries they are available from local production. In addition they also have many disadvantages. Their quality and composition is likely to be less constant than industrial produced oils. Also, they may be unstable and turn rancid upon storage. Like waxes, oils are good solvents for many drugs and preservatives. Preservative inactivation by oils is especially important at tropical storage temperatures.

Paraffins are chemically indifferent and stable. They are far less efficient solvents for most drugs and preservatives. Paraffins are relatively cheap. Paraffin creams have less penetrating power and are greasier on the skin.

Side effects resulting from the oily phase components of oil-in-water creams are rare. Some components (e.g., sesame oil) are better avoided as they have a high sensitisation potential. In rare cases yellow petrolatum causes sensitisation. Poor quality white petrolatum may cause irritation on the skin because it contains traces of a bleaching agent. For reasons of general availability, low price, stability and indifference towards most drugs and preservatives, we consider paraffins most appropriate for cream production.

5.4.4 The water phase

Water is generally used as the hydrophilic phase in creams. Preservatives are used to prevent microbial problems (see paragraph 5.4.6). Humectants such as glycerol, propylene glycol or sorbitol are added to prevent evaporation of water.

Evaporation occurs in stored creams (stability problem) and after application (therapeutical problem). It depends on the surface area and surface properties, and environmental factors such as humidity and temperature. Environmental conditions usually cannot be changed but manipulation of the cream properties is possible. For example evaporation from a capillary system is diminished with smaller capillaries.

After applying a cream on the skin, water will evaporate and an oily layer remains. This layer also contains the active ingredient. When high quantities of powder are processed in the cream (as for example in sulphur cream) the result is a thick layer quite similar to a paste with a relatively high concentration of active ingredient. This has some occlusive and therefore moisturising effects, but it can also have a drying effect, depending on the type and amount of oil or fat used. When paraffins are used in relatively large proportions as in the basic cream in this formulary, the resulting cream has mild moisturising effects and adding humectants is not necessary for therapeutic reasons.

The evaporation of water from stored creams results in an oily layer on top of the cream, which prevents further evaporation. Unfortunately, this only happens when half of the water has evaporated and hence it is not considered a protective mechanism. We studied water evaporation from different versions of basic cream. We found no significant differences in evaporation between creams without humectant, with 4% sorbitol, and with 10% propylene glycol. The evaporation losses were determined in open jars (diameter 49 mm) containing 10.0 g cream and stored at 45 °C. We concluded that water evaporation was essentially similar between the three creams (unpublished results). Although evaporation is a poorly reproducible process, it is concluded that humectants are unlikely to prevent a stored cream from drying out. As these ingredients are also expensive we do not recommend their use.

5.4.5 Emulsifiers

Emulsifiers are characterised by the hydrophile/lipophile balance (HLB). The HLB value is defined as the hydrophile percentage of the molecule divided by 5. Depending on the type of emulsion desired, the required HLB value of the emulsifier is calculated. However, hydrophilicity is not the only point to consider. The shape of the emulsifier is also important as the molecule must fit into the interface (25). The form and required HLB are also related to droplet size. The smaller the droplets, the more convex the interface is. Therefore with smaller droplets, the lipophilic part must also be smaller. The reverse is also true; using an emulsifier with a higher HLB value – and thus a smaller lipophilic part – produces a cream with smaller droplets.

Optimal stability of a cream results from mixtures consisting of a hydrophilic emulsifier (high HLB) and a lipophilic co-emulsifier (low HLB). Cetostearyl alcohol is one of the most widely used co-emulsifiers (e.g., in lanette wax and cetomacrogol wax) because it exists in the α-modification over a wide temperature range. As discussed in paragraph 5.2.7 the α-modification produces the best stabilisation of oil-in-water creams (6).

The hydrophilic part of the emulsifier is hydrated which means that it is surrounded by water molecules. This causes the hydrophilic part to be much bigger than expected. At higher temperatures the hydration will diminish, the hydrophilic part will become smaller, and the HLB and emulsifying efficiency are affected. High temperatures therefore lead to separation of the cream. The temperature at which this happens is called the phase inversion temperature. Very strong hydrophilic emulsifiers like sodium lauryl sulphate do not show phase inversion at temperatures below 100 °C (26,27).

At higher temperatures other stability problems are also important. A cream has many different (gel) phases and phase transitions result in rheological changes. This causes or enhances the creaming tendency. Both creaming and separation result in inhomogeneous creams. Creams therefore require mixing or stirring after exposure to high temperatures. The basic cream in the formulary was stable at 45 °C for 3 months, and at 70 °C for 2 weeks. At 70 °C some creaming occurs but this is a slow process (unpublished results). Water evaporation at these temperatures is a problem and the packaging must be impermeable for water or water vapours.

The high hydrophilicity of lanette wax (sodium lauryl sulphate 10% and cetostearyl alcohol 90%) and the high thermo stability of the resulting creams defines lanette wax as most appropriate emulsifier. Irritation develops more rapidly than with cetomacrogol creams but is uncommon. Incompatibilities of drugs form a more serious problem with cetomacrogol wax than with lanette wax, as many phenolic compounds that are essential drugs (salicylic acid, dithranol and others) are incompatible with cetomacrogol. Larger cations (e.g., tetracycline hydrochloride) are incompatible with lanette wax (sodium lauryl sulphate) but such drugs are not included in the formulary.

5.4.6 Preservation

Oil-in-water creams are microbiologically vulnerable. Water forms a continuous phase and micro-organisms spread throughout the cream. Water and nutrients are available. Some micro-organisms use cetostearyl alcohol as a nutrient and creams become growth promoting media. Collapsible tubes are good packagings to prevent contamination, but are less suitable in tropical regions as they are expensive and for single use only. Also the contents cannot be inspected and stirred if necessary. Jars offer only poor protection against contamination. The water phase of a cream therefore requires adequate preservation. Only a few preservatives are appropriate. The main problems with preservatives are inactivation and the occurrence of side effects.

5.4.7 Inactivation of preservatives

Inactivation of preservatives results from various constituents of the cream or packaging. Only unbound preservative that is dissolved in the water phase is active. The concentration (which is related to the distribution ratio), adsorption and dissociation are factors affecting efficacy of the preservative, while degradation and precipitation are inactivating processes.

The distribution of the preservative between the oil and water phases depends on its solubility in oil and water. Distribution ratios determine the relative concentrations in the various phases. Paraffins are

poor solvents for most preservatives and reaching an effective concentration of the preservative in the water phase is not a problem. Good solvents, such as oils and waxes, should be avoided. The actual concentration in the aqueous phase is also determined by the amount of lipid present. Solubility and thus distribution depend on the temperature. Distribution ratios rise with increasing temperatures, and active concentrations therefore are less at higher temperatures (28).

Emulsifiers inhibit preservatives by two mechanisms: molecular adsorption and uptake into micelles. A distinction between the two is not always possible, but is useful to enable the prediction of temperature influences. Inactivation caused by adsorption is less at higher temperatures, but inactivation caused by changes in distribution between the phases is higher. Non-ionics such as cetomacrogol are more potent inactivators than anionics such as lauryl sulphate (29). Preservative inactivation by emulsifiers can be very effective.

Acidic preservatives are active in the undissociated form and can therefore only be used over a small pH range (sorbic acid below pH 5, phenol below pH 9.5). In addition the pH influences the stability of preservatives. The influence of temperature on dissociation is extremely complex. All chemical equilibriums shift with changing temperatures, including the dissociation of water and preservatives. At regular storage temperatures this effect is small unless appreciable amounts of preservative are already dissociated.

Adsorption of preservatives to solids plays a role in deactivation (30-32). Most creams do not contain large amounts of solids but adsorption to packaging materials can occur. Adsorption is less at higher temperatures and is therefore not a problem of tropical climates.

Instability and decomposition cause inactivation of preservatives, but also the formation of toxic degradation products. The pH and temperature are relevant factors for degradation. Degradation is faster at higher temperatures (see paragraph 9.1). Packaging materials influence decomposition (31,32).

Temperature strongly influences the inactivation mechanisms and the intrinsic activity of preservatives. The intrinsic activity is higher at higher temperatures. The overall effects of all these changes on the total activity is very difficult to predict. In some cases increased activity of the unbound fraction even compensated for increased inactivation (28).

5.4.8 Side effects of preservatives

The most frequently occurring side effects of preservatives are sensitisation and irritation. Risk assessment is based on the number of side effects reported in literature. Additionally the level of utilisation of preservatives needs to be taken into account as this is a major factor determining the prevalence of side effects. For example methylparaben has long been considered a notorious sensitiser, but De Groot places this effect in the context of its wide spread use and concludes that methylparaben is relatively safe (33).

It has been reported that black skin is less vulnerable to sensitisation than white skin. This effect was demonstrated for a limited number of chemical substances but was not found for many others. Black skin is as thick as white skin but the stratum corneum consists of more cell layers and hence is more resistant to irritation. The largest differences are expected for irritating chemicals. Some authors, however, argue that the supposed difference between black and white skin does not exist at all. They

explain inconsistent study results by pointing at the difficulties of detecting minimal redness on the skin of black people (34,35).

5.4.9 Choosing a preservative

Many preservatives are available for dermatologicals and cosmetics. Parabens are the most widely used. In choosing a preservative the main points to consider are intrinsic activity (broad spectrum, lack of resistance), compatibility with the cream system, lack of side effects (toxicity, irritation, sensitisation), and stability.

The emergence of bacterial resistance can be a problem but is very difficult to predict. Resistance develops when preservatives are used on a large scale, and the more they are used the more resistance is reported.

Some drugs such as chlorhexidine have preservative and antiseptic properties. Although this may seem convenient because only one raw material is required, it is inappropriate because resistance problems are even more serious when they also preclude a drug from therapeutic use.

Cationic preservatives (cetrimide, benzalkonium chloride) show various incompatibilities with the systems that are preserved (e.g., lanette wax) and are better avoided. Sorbic acid may cause irritation, it is only active below pH 5, and is unstable (see paragraph 9.7) but compatible with most cream systems. Various phenolic compounds (e.g., chlorocresol) are generally less tolerated and not very stable (see paragraph 9.6). Mercury compounds are obsolete for dermatological use because they are very toxic and have harmful environmental effects.

Propylene glycol is compatible with most cream systems and is generally suitable as preservative. In its usual concentration (10%) it is well tolerated but causes irritation at higher concentrations. Propylene glycol is stable. It enhances the penetration of various drugs (e.g., corticosteroids). Preservation with propylene glycol is quite expensive as high concentrations are required.

Methylparaben appears the best choice (36). It is reasonably stable although hydrolysis occurs (see paragraph 9.2). It has good activity, is well tolerated and compatible with the basic cream in this formulary but not with creams containing vegetable oils (28). It is perhaps the most widely used preservative in dermatologicals and cosmetics, and its side effects and other properties are well documented. Sensitisation occurs but is not very common with the concentrations generally used (37). It is used over a large pH range but stability is best at pH 4 to 5 (see paragraph 9.2). Methylparaben is cheap especially when the concentration required is taken into account.

5.4.10 Preparation methods

The preparation method is one of the factors determining the stability of a cream. Crystallisation of the emulsifier is influenced by the cooling rate, the droplet size by the mixing efficiency and the mixing temperature. Cold emulsification produces a homogeneous emulsion but the product is not stable enough. If the cream is not well stirred during cooling, a less stable cream will result (unpublished results). Care should thus be taken that the preparation methods ensure a stable product. The preparation methods in most formularies, including this one, are generally for small scale production up to 1 kg. When production is scaled up, for example to a capacity of preparing 10 kg in a batch, both the mixing efficiency and the cooling rate are affected. In large scale production it is necessary to check whether the resulting creams are stable enough.

5.4.11 Conclusions

A simple and stable cream for use in tropical conditions is obtained with the following formula: lanette wax SX 15%, paraffin 35%, methylparaben 0.15%, water to 100%. Other, less appropriate preservatives are sorbic acid (unstable) and propylene glycol (expensive).

The cream requires packaging that allows stirring and prevents evaporation of water. After prolonged storage or after storage at high temperatures, for example during transport, creams require stirring before dispensing or use.

5.5 Shake lotions

5.5.1 Introduction

Shake lotions contain a certain amount of solid substance (powder). Here we focus on shake lotions consisting of a powder and a water phase. Upon application to the skin the water evaporates which results in a cooling effect. The powder in the lotion enhances this effect by enlarging the surface area from which evaporation takes place. Shake lotions have general soothing and weak astringent properties.

Various drugs can be added but in our opinion only the antipruritic shake lotion, also known as calamine lotion, is essential. Corticosteroids can be added but this negatively affects the stability of the lotion. Tars are better processed in pastes, creams or solutions.

Calamine lotion is widely used and considered an essential drug by the World Health Organization (WHO). The properties of the lotion with 0.5% phenol make it suitable for use in tropical conditions. From a microbial and physical perspective it is stable, and it has cooling, antipruritic, weak astringent and weak antiseptic effects. Other shake lotions are microbiologically more vulnerable or contain raw materials that are less appropriate for production in less developed and resource scarce regions. Various common ingredients of shake lotions are better avoided as they may cause side effects. Talc for example causes granulomas when used on damaged skin. This is due to the presence of crystalline silicates in specific modifications in the talc. The same effects are known from other silicates such as asbestos. Natural clays such as bentonite do not contain these modifications and are safe in this respect and preferred. Starch is not suitable because it is often contaminated with micro-organisms. Zinc is absorbed from wounds but the relevance of this effect in clinical practice is questionable (20,38). When used on large parts of the body or on damaged skin phenol is absorbed and causes systemic side effects. Therefore calamine lotion should not be used on open wounds.

5.5.2 Composition of calamine lotion

The recipe of the *British Pharmacopoeia* (7) and several other pharmacopoeias for calamine lotion is per 100 ml: calamine 15 g, zinc oxide 5 g, veegum 3 g, sodium citrate 0.5 g, glycerin 5 ml, liquefied phenol 0.5 ml and water. Some of these ingredients are essential whereas others can be substituted for cheaper ones.

According to the *British Pharmacopoeia* calamine is basic zinc carbonate with 2% ferrous oxide and according to the *United States Pharmacopeia* it is zinc oxide with 2% ferrous oxide. The two materials are considered equivalent. Ferrous oxide colours the mixture to match the colour of white skin and makes the preparation cosmetically acceptable. For people with a dark skin this is inadequate. Zinc oxide can be used instead of calamine without affecting the properties of the lotion.

Veegum is a standardised preparation in contrast to bentonite. The bentonites currently available for pharmaceutical use have adequate quality and are suitable. Glycerin is required for the trituration (see paragraph 8.4.2) of the bentonite and zinc oxide. When highly efficient mixers are available glycerin can be left out, but this is unlikely in small scale production units in developing regions. Therefore we consider glycerin an essential ingredient of calamine lotion. Sodium citrate controls flocculation in the suspension system and is essential to obtain a stable and pourable suspension. The trisodium citrate is used for this purpose. Other citrates can also be used but enhance dissolution of zinc oxide (39). It is unclear whether this is a problem in clinical practice. Trisodium citrate salt is also used for oral rehydration and is therefore widely available. For this reason we recommend to use this specific salt.

We consider the following formula for calamine lotion most appropriate: zinc oxide 20 g, bentonite 3 g, sodium citrate 0.5 g, glycerin 5 ml, liquefied phenol 0.5 ml and water to 100 ml. Although this preparation contains no calamine, we comply with the generally used name. An alternative is to call it 'modified calamine lotion' to distinguish it from the calamine lotion in the various pharmacopoeias.

5.5.3 Sedimentation

Most pharmaceutical suspensions separate during storage as the result of sedimentation of the solid substance. Controlling this process is required by slowing it down and making the sediment easily resuspendable.

Sedimentation depends mainly on the differences in specific gravity of the particles and the fluid phase, the size of the particles, and the rheological properties of the fluid phase. Sedimentation is slower when:
- The particles are smaller.
- The viscosity of the liquid phase is greater.

In calamine lotion the bentonite is used to increase the viscosity.

Resuspendability of the lotion depends mainly on how the suspended particles are packed. The bigger the particles, the looser the sediment and the better the resuspendability. The particles may associate (flocculate) to form bigger clusters. Such clusters deposit more rapidly but are easier to resuspend. Controlled flocculation is often used in the formulation of pharmaceutical suspensions as a way to control sedimentation and resuspendability. This is also the case for the modified calamine lotion in this formulary. Sodium citrate acts as a partial deflocculating agent. From the results of our experiments (unpublished results) we concluded that the sedimentation process is somewhat faster at higher temperatures (we tested 30 °C, 37 °C and 45 °C), but still very slow, and that the resuspendability remains good. Therefore the modified calamine lotion is appropriate for use in tropical conditions.

5.5.4 Preservation

Modified calamine lotion is preserved with phenol which has additional antipruritic and antiseptic properties. The high pH of the lotion and the presence of large amounts of solid substance with a high absorptive power (bentonite) prohibit the use of most other preservatives. Three mechanisms decrease the preservative activity of phenol: dissociation, adsorption and degradation (see paragraph 9.6).

Only undissociated phenol is active (30). The pH of modified calamine lotion is 9.1; for other calamine lotions values up to pH 9.5 were reported. At 20 °C and a pH of 9.1 85.5% of the phenol is undissociated, at pH 9.5 this is 71.1%. The influence of temperature is difficult to predict but is limited. At a pH of 9 to 9.5 some bacteria are still viable and at higher pH values bacterial growth is even less

and does not form a problem (40). Phenol is thus adequate for the preservation of aqueous solutions with such high pH values.

Adsorption to particles is an important inactivation mechanism for preservatives. Bentonite is a good absorbent for preservatives, but more specifically for cationic substances. We determined the adsorption of phenol to the powder phase of the modified calamine lotion. Adsorption was practically non-existent (unpublished results) and phenol is a suitable preservative for the modified calamine lotion in this formulary. Adsorption is less at higher temperatures and is therefore unlikely to be a problem in tropical climates.

Liquefied phenol is preferred over pure phenol because it is easier to process. It contains approximately 80 to 90% phenol. The resulting free concentrations of undissociated phenol in the lotion will not be lower than 0.3% which is considered appropriate.

5.5.5 Conclusion

The proposed formula for calamine lotion is appropriate for tropical conditions. It is cheaper than the original formula of the *British Pharmacopoeia* and other pharmacopoeias, but has the same therapeutical properties. The original formula is also appropriate for the tropics because it is adequately preserved.

5.6 General references

As a general reference for this chapter we used the book *Aulton's Pharmaceutics* (12). The *Pharmaceutical Codex* is a valuable reference for all aspects of pharmaceutical compounding and dispensing (41). Another valuable reference on active and other ingredients is *Martindale's Extra Pharmacopoeia* (17). As the preparations in the dermatological formulary often contain ingredients that have been used for long periods of time, older editions of the *Martindale* suffice. Finally, the website "*e-drug compounding (www.openapo.info)*" gives more preparation formulae and other useful information (42). We prefer the "good old" preparations that have been used over time, are well known and robust, easy to prepare and relatively affordable. Surprisingly little new information has been published on these preparations so we keep referring to the original but sometimes rather old literature with regard to their composition and preparation.

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6 Basic standards of Good Manufacturing Practice

6.1 Introduction

Quality assurance is an important issue in manufacturing medicinal preparations. Good quality of a pharmaceutical product means that the properties and characteristics comply with a number of predefined and up-to-date standards. In this way the patient can always rely on the product as it is of good and constant quality and safe to use. Quality assurance in pharmaceutical manufacturing processes demands a permanent commitment and contribution of all persons involved.

In the pharmaceutical industry the guidelines for Good Manufacturing Practice (GMP) are leading. They outline the principles of quality assurance for the production of medicines for humans and animals. Under different circumstances the GMP guidelines are interpreted to fit the context in which the manufacturing takes place. In practice, the interpretation of GMP standards in a local production unit will differ considerably from the strict interpretation in the pharmaceutical industry.

GMP guidelines are regularly updated. The most recent versions of the guidelines as well as other relevant documents can be found on the website of EudraLex, http://ec.europa.eu/health/documents/eudralex/.

6.2 GMP

In this chapter we list the GMP issues most pertinent to local production in developing countries and regions.

6.2.1 Personnel

a. Each unit should have a responsible person approved by the authorities. Preferably, there should be separate heads for manufacture and control. The number of employees should be sufficient to ensure the quality of the products. They need to comply with the instructions.
b. All personnel should be properly trained and instructed with respect to their tasks.
c. Immediately upon appointment all personnel should be given written instructions concerning:
   - the organisation of the unit;
   - rules and formats for labelling;
   - procedures in case of mistakes and problems;
   - safety precautions to be taken when handling toxic or dangerous materials, emergency rules (fire etc.);
   - personal hygiene (compare 6.2.2 Hygiene).
d. All employees must sign a written statement declaring that they have taken notice of all instructions.

6.2.2 Hygiene

a. High standards of personal cleanliness should be observed by all people concerned with production processes.
b. Hand-washing and hygienic drying facilities should be available to, and used by, manufacturing personnel (compare 6.2.3 Premises). Direct contact should be avoided between the operator's hands and raw materials (ingredients), intermediates and end products.
c. All personnel entering production areas should wear adequate clothing. Clothing should be clean and should not be worn outside the production unit.
d. Personnel should report infections and skin lesions to the staff, and a defined procedure should be followed when such reports have been made.
e. Eating, drinking, chewing and smoking should be confined to a separate room, which is not being used for other purposes.

6.2.3 Premises

a. Premises should be of a suitable construction, sufficient size and adequately adapted to their intended use.
b. Premises should be suitably illuminated and ventilated. The working areas should have a sufficient size to allow efficient organisation of the manufacturing, and to minimize the risk of mix-ups and cross-contamination.
c. The premises should include adequate accommodation for changing clothes, washing and toilet purposes.
d. The premises should be constructed and equipped so that they can be easily cleaned and, if necessary, disinfected. Cleaning and disinfection should occur according to written instructions. The premises should be kept free from insects, pests, rodents or other animals.

6.2.4 Equipment

a. All equipment used in manufacture or quality control should be regularly inspected to ensure its proper functioning.
b. All equipment must be safe. Operating and cleaning instructions should be in the immediate vicinity of the apparatus.
c. Weighing and measuring equipment should be accurate and, if necessary, should be regularly calibrated.
d. Manufacturing equipment should be suitable for its purpose, easy to clean, and non-reactive to the materials employed.

6.2.5 Manufacturing procedures for large scale production

a. There should be a master production form for each product, stating its components and procedures for manufacturing and quality control. Each batch should be produced according to a batch production form. This batch production form is a true copy or authorized transcript of the master production form. All relevant information obtained during the production process (measurements, readings and batch numbers of the raw materials) should be recorded on this batch production form. All batch production forms should be filed for a specified period of time.
b. All components, intermediates and products should be identifiable throughout the whole production process.
c. All components must comply with their particular specifications and be labelled with the name designated in the specification before being released for use. The same name should be used in the master production form and batch production form.
d. Liquids, creams and ointments should be manufactured in such a way that microbial contamination is avoided.

e. Water used for the production of dermatological (topical) preparations should be of at least potable quality and have a low microbial count.
f. All finished products should be identified by labels that should bear at least the following information:
   – name of the unit;
   – name of the product as given in the master production form;
   – batch number;
   – production date;
   – expiry date.

6.2.6 Manufacturing procedures for extemporaneous preparation and dispensing

a. There should be a master production form stating components and production procedures for each preparation.
b. All relevant information obtained during the production process should be recorded, preferably on the doctor's prescription. These records should be filed during a specified period of time.
c. All components, intermediates and products should be immediately processed or be identifiable until processed.
d. Liquids, creams and ointments should be manufactured in such a way that microbial contamination is avoided.
e. Water used for the production of dermatological preparations should be at least of potable quality and have a low microbial count.
f. Finished products that are not immediately handed out to the patient should be identified by labels that should bear at least the following information:
   – name of the unit;
   – name of the preparation;
   – date of production;
   – name of the patient.
g. When preparations are delivered to the patient, measures should be taken to ensure that:
   – the right preparation is delivered to the right patient in the right quantity;
   – the preparation complies with all legal requirements;
   – the patient is properly instructed about application of the drug. Personnel assigned to this task should be properly trained.

7 General notes on production

7.1 How much to prepare

The formulation and preparation methods in the preparation monographs of chapter 12 are written for a standard quantity of 100 g or 100 ml. Other quantities can also be prepared. Then proceed as follows:

1. Determine the multiplication factor. This is the quantity desired divided by the standard quantity.
2. Multiply the quantity of each ingredient by this multiplication factor.

An example:
You want to prepare 500 g emulsifying ointment.
The multiplication factor is 500/100 = 5. What you need is: lanette wax 5 x 30 g = 150 g, liquid paraffin 5 x 25 g = 125 g, petrolatum 5 x 45 g = 225 g.

To produce larger batches all quantities in the formulation section of the monograph need to be multiplied by the multiplication factor. However, the evaporation losses when water is boiled, are relatively smaller when boiling larger quantities. Therefore, the excess of water that has to be boiled and cooled down is relatively less when batches of more than 500 g or 500 ml are made.

The preparation methods in this book are adjusted to simple, small scale production of medicines. In general this means manual production without machines. Larger quantities cannot always be prepared manually and machines are required. Some of the preparation methods need adapting to machine production for example because the mixing efficiency is different. As a general rule, quantities up to 1 kilogram or 1 litre can be prepared manually. Thirty-five master production forms for stock preparations of 1 kg or 1 litre are included on the cd that comes with the book. They can also be found on the internet via www.rug.nl/wewi/dermatology or directly at http://irs.ub.rug.nl/dbi/4fed64994b40a. We consider these preparations suitable for local production, dispensing and use in the least developed regions and countries around the world.

7.2 Quality assurance

The quality assurance of a preparation cannot solely be based on the final control of the end product. As quality control frequently involves destructive examination of the sample, it is practically impossible to examine every product of a batch because it would leave nothing to dispense. The overall quality of a drug is determined by the pharmaceutical design and the manufacturing process, and encompasses the skills of

Product name		Batch quantity	Master manufacturing formula approved by
Prepared by :			
Preparation date:			Source master manufacturing formula: Dermatological preparations for the tropics, 2nd ed.
Batch number:			

Raw materials and packaging materials

	Quantity prescribed	Source and batch number	Actual quantity weighed/measured	Initials weighing	Initials control
Raw material 1					
Raw material 2					
Raw material 3					
Raw material 4					
Raw material 5					
Raw material 6					
Raw material 7					
Raw material 8					
Raw material 9					
Raw material 10					
Packaging material 1					
Packaging material 2					

Preparation	**In-process checks**	
Preparation method step 1	In-process check 1	
Preparation method step 2	In-process check 2	
Preparation method step 3	In-process check 3	
Preparation method step 4	In-process check 4	
Preparation method step 5	In-process check 5	
Preparation method step 6	In-process check 6	
Preparation method step 7	In-process check 7	
Preparation method step 8	In-process check 8	
Preparation method step 9	In-process check 9	
Preparation method step 10	In-process check 10	
Preparation method step 11	In-process check 11	
Preparation method step 12	In-process check 12	
Preparation method step 13	In-process check 13	
Preparation method step 14	In-process check 14	
Preparation method step 15	In-process check 15	

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Storage condition		Yield	
Shelf life		Loss	
Expiry date		Loss due to	

End controls before release of batch	Checked by	Result
Batch numbers raw materials correct?		
Packaging materials correct, in good condition and closed properly?		
Labelling conform model?		
Expiry date stated correctly?		
Specific product requirement 1 fulfilled?		
Specific product requirement 2 fulfilled?		
Are all boxes of this form filled correctly and completely?		

Batch released by (name and signature)		Date:	

Model of label for stock

For external use only
Product name
Batch number and batch date
Do not use past: (expiry date)
Storage conditions
Safety precautions

Model of label for the patient

For external use only
Dispensing unit and date
Product name and quantity
Patient name
Dosage information and instructions for correct use
Safety precautions
Do not use past (expiry date or dispensing date + period of safe use)

Figure 7.1. Model of a master production form

the person who manufactures. End product control is always necessary, in-process controls are included in each preparation to avoid mistakes and poor quality. In-process controls are part of GMP, Good Manufacturing Practices (see chapter 6). This way of working is much preferred over "allowing" mistakes and trying to identify faulty products with an end control.
GMP that includes in-process controls is even more important when facilities for end product control are poor or lacking, as may be the case in developing countries or regions. Therefore, a set of basic standards for good manufacturing practice at local production units in tropical countries is included in chapter 6 of this formulary. These standards are adjusted to the situation in developing regions and concern personnel, hygiene, buildings, equipment and preparation procedures. The importance of people in this respect cannot be overemphasized. Poor quality of drugs is most often due to human error or even carelessness.

7.3 Production forms

Basic standards for GMP also include rules for administration and labelling. This is a very important aspect. Master production forms need to be developed for each preparation that will be made. The forms should be fairly detailed, and always adjusted to the specific local situation, taking into account the usual batch size, preparation method, available apparatus, etc. For each stock preparation a batch production form needs to be filled in and kept in file. A model master production form and an example to prepare a batch of 1 litre calamine lotion are found in figure 7.1 and 7.2. A practical method is to make a print or copy of the master production form prior to starting the manufacturing of a new batch. All production details for that specific batch are written down on the form and checked before releasing the batch for stock or dispensing. Figure 7.3 shows an example of such a fully completed batch production form. The master production forms also provide models of labels for stock storage, as well as models of labels for the patient.

Preparations that are directly dispensed to the patient on doctor's prescriptions also require recording and filing. All production details for that specific preparation are written down on the form and checked before releasing and dispensing.

7.4 Packaging

Packaging is essential to protect the preparation from adverse environmental influences. In the preparation and raw material monographs (chapters 12 and 13) the optimal type of packaging is specified. In daily practice however the optimum is not always possible. When suboptimal packaging is used the shelf life is shorter.

In general the following packaging is suitable for dermatological preparations:
- glass or polyethylene bottles for fluids
- polyethylene jars for semisolids (creams, ointments).

Jars made of glass are also suitable containers but are a little more expensive, heavier, and more fragile. Jars with a wide opening are practical to allow stirring when the preparation has become inhomogeneous. Such jars are also easily cleaned for reuse. A deposit system can be set up for return of empty jars and bottles.

Calamine lotion | Batch quantity 1000ml | Master manufacturing formula approved by

Prepared by :
Preparation date:
Batch number:

Source master manufacturing formula: Dermatological preparations for the tropics, 2nd ed. (modified from BP)

Raw materials and packaging materials

	Quantity prescribed	Source and batch number	Actual quantity weighed/measured	Initials weighing	Initials control
Zinc oxide	200 g				
Bentonite	30 g				
Trisodium citrate (.$2H_2O$)	5 g				
Glycerine	50 ml				
Liquified phenol	5 ml				
Water	to 1000 ml				
Dark coloured glass bottle of 1000 ml	1				

Preparation	**In-process checks**	
1.Boil 1000 ml water for 1 minute and allow to cool. Use this water for the preparation.	Water boiled?	yes/no
2.Calibrate the glass bottle for 1000 ml.	Calibration control	
3.Dissolve the trisodium citrate in 700 ml water.	Completely dissolved?	yes/no
4.Mix the zinc oxide with the bentonite in a mortar.		
5.Triturate this zinc oxide/bentonite mixture with the glycerine and 200 ml of the citrate solution.		
6.Add the rest of the citrate solution and mix until homogeneous.	Homogeneous?	yes/no
7.Add the liquified phenol and mix.		
8.Put the mixture in the calibrated bottle.		
9.Rinse the mortar with a little water and add to the calibrated bottle.		
10.Add sufficient water to produce 1000 ml lotion.	Total volume?	
11.Close the bottle properly and mix until homogeneous.	Homogeneous?	yes/no

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Storage condition: below 40°C, protect from direct sunlight
Shelf life: 3 months
Expiry date
Yield
Loss
Loss due to

End controls before release of batch	Checked by	Result
Batch numbers raw materials correct?		
Packaging materials correct, in good condition and closed properly?		
Labelling conform model label for stock?		
Expiry date stated correctly?		
Bottle closed properly?		
Lotion homogeneous?		
Are all boxes of this form filled correctly and completely?		

Batch released by (name and signature) Date:

Model of label for stock

For external use only
Calamine lotion
Batch number and batch date
Do not use past: (production date + 3 months)
Storage below 40°C, protect from direct sunlight
Shake well before dispensing

Model of label for the patient

For external use only
Dispensing unit and date
Calamine lotion _____ ml
Patient name
Shake well before use. Paint the lotion on the skin ___ times daily and allow to dry. Do not cover
Do not use past: (dispensing date + 1 month)

Figure 7.2. Example of a master production form: Calamine lotion

Frequent reopening and stirring the contents of jars increases the risk of microbial contamination. The preparations for this formulary were specifically selected for optimal microbial and physical stability. Information on the susceptibility of the preparations for microbial contamination and how to deal with physical instability, for example sedimentation of suspensions, or bleeding of petrolatum, is found in the monographs.

Some preparations need protection from light. This is done by packing them in a suitable dark coloured container. Storage in a dark place is equally effective. The storage containers can also be wrapped in a piece of dark paper or cloth.

Some preparations, for example dithranol cream, require an airtight container. Glass containers with a tightly fitted screw cap are the most suitable. Zinc oil reacts with certain plastics, including polyethylene. For this reason zinc oil preparations require packaging and storage in glass containers.

Collapsible tubes have certain advantages. They provide adequate protection against microbial contamination and light and are also airtight. A disadvantage is that they are expensive and not reusable. When a preparation becomes inhomogeneous it goes unnoticed and stirring the contents is impossible. Therefore collapsible tubes are generally regarded unsuitable for use in hot climates.

7.5 Labelling

It is essential that all drugs, preparations and raw materials are adequately labelled. Labelling raw materials is generally done by the producer of the materials. For optimal stock control it is advisable to provide raw materials and preparations with a label stating the date of their receipt.

Labelling the preparations should be done immediately after packaging. Stock preparations need a label containing the following information:
- full name of the preparation
- preparation date
- batch number (corresponding with the batch number on the production form)
- expiry date ("should not be used past dd/mm/yyyy")
- storage conditions
- required dispensing information, such as "shake before dispensing or use" or "mix before dispensing or use"
- warnings in case of toxic or hazardous preparations.

When dispensing a preparation the following information needs to be written on the label:
- name of the patient
- "for external use only"
- name of the preparation
- dose and instructions for use (including: to be stirred, shaken), pictograms can be useful for patients who cannot read
- dispensing date
- expiry date ("do not use past dd/mm/yyyy")
- warnings in case of toxic or hazardous preparations.

Calamine lotion | Batch quantity 1000ml | Master manufacturing formula approved by F. Ngoma, Chief Pharm.

Prepared by :	X. Johnson
Preparation date:	April 11 2012
Batch number:	12DER-041101

Source master manufacturing formula: Dermatological preparations for the tropics, 2nd ed. (modified from BP)

Raw materials and packaging materials

	Quantity prescribed	Source and batch number	Actual quantity weighed/measured	Initials weighing	Initials control
Zinc oxide	200 g	IDA-230406	200.01 g	XJ	~~FN~~
Bentonite	30 g	IDA-540987	30.04 g	XJ	~~FN~~
Trisodium citrate (.$2H_2O$)	5 g	IDF-11/765	5.00 g	XJ	~~FN~~
Glycerine	50 ml	IDA-769854	50.0 ml	XJ	~~FN~~
Liquified phenol	5 ml	IDF-12/003	5.00 ml	XJ	~~FN~~
Water	to 1000 ml	TAP Water	See ip check		~~FN~~
Dark coloured glass bottle of 1000 ml	1	LOA-1201	1	XJ	~~FN~~

Preparation | **In-process checks**

1.Boil 1000 ml water for 1 minute and allow to cool. Use this water for the preparation.	Water boiled?	yes/~~no~~ XJ
2.Calibrate the glass bottle for 1000 ml.	Calibration control	~~FN~~
3.Dissolve the trisodium citrate in 700 ml water.	Completely dissolved?	yes/~~no~~ XJ
4.Mix the zinc oxide with the bentonite in a mortar.		
5.Triturate this zinc oxide/bentonite mixture with the glycerine and 200 ml of the citrate solution.		
6.Add the rest of the citrate solution and mix until homogeneous.	Homogeneous?	yes/~~no~~ XJ
7.Add the liquified phenol and mix.		
8.Put the mixture in the calibrated bottle.		
9.Rinse the mortar with a little water and add to the calibrated bottle.		
10.Add sufficient water to produce 1000 ml lotion.	Total volume?	1000 ml FN
11.Close the bottle properly and mix until homogeneous.	Homogeneous?	yes/~~no~~ XJ

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Storage condition:	below 40°C protect from direct sunlight	Yield	1000 ml XJ FN
Shelf life:	3 months	Loss	NONE
Expiry date	JULY 11 2012	Loss due to	NOT APPLICABLE

End controls before release of batch

	Checked by	Result
Batch numbers raw materials correct?	~~FN~~	CORRECT
Packaging materials correct, in good condition and closed properly?	~~FN~~	CORRECT
Labelling conform model label for stock?	~~FN~~	CORRECT
Expiry date stated correctly?	~~FN~~	CORRECT
Bottle closed properly?	~~FN~~	CORRECT
Lotion homogeneous?	~~FN~~	CORRECT
Are all boxes of this form filled correctly and completely?	~~FN~~	CORRECT

Batch released by (name and signature): F. Ngoma (chief Pharm) Fred NgoMa | Date: April 11th 2012

Model of label for stock

For external use only
Calamine lotion
12DER-041101
Do not use past: july 11th 2012
Storage below 40°C, protect from direct sunlight
Shake well before dispensing

Model of label for the patient

For external use only
Dispensing unit and date
Calamine lotion _____ ml
Patient name
Shake well before use. Paint the lotion on the skin ___ times daily and allow to dry. Do not cover
Do not use past: (dispensing date + 1 month)

Figure 7.3. Example of a completely filled batch production form of a batch of Calamine lotion

7.6 Storage

For the storage of drugs and preparations a cool, dark and dry place is always best. This does not mean, however, that all drugs have to be kept in a refrigerator or that special storage rooms are always necessary.

General recommendations are:

a. A dark, cool and dry place is preferred.
b. The stock room should be kept clean and free from insects, rodents etc., which also means that no food and drinks are allowed in the stock room.
c. Drugs should be stored orderly:
   - to avoid accidents, drugs for external use should be kept apart from other types of drugs such as tablets;
   - all drugs require proper labelling;
   - all drugs should be stored in alphabetical order;
   - new articles should be put behind the old stock to make sure that the old stock is used first (this is the "first in, first out" principle).
d. Secure the drugs against theft.

7.7 Stock control and shelf life

Stock control of medicines is as difficult as it is important. A certain amount of medicines should be held in stock for dispensing on demand. However, when the stock is too large the medicines are stored too long and expire.

The preparation monographs in chapter 12 include information on the period of time after manufacturing in which the preparations are safely used. This period consists of two parts, i.e., the shelf life at the production unit, the medical store, or the dispensary, and the time it is used at the patient's home or in the hospital. This second part of the shelf life, at the patient's home, depends on the quantity that is supplied, the dosage regimen and the duration of the therapy. Since the time of use can only be estimated, dermatological preparations should be dispensed well before they reach the expiry date, thereby allowing a reasonable shelf life at the patient's home. This reasoning implies that the quantity dispensed to a patient should be reasonable and not too large (see table 3.2 to establish reasonable quantities for dispensing).

The quantity of medicines in stock should be large enough not to run out before new stock arrives or a new batch is prepared. A sensible way for stock control is probably to produce smaller batches at a time and to do this more often. For stock control record keeping of the quantities of medicines prepared and dispensed is essential. When this has been done over a longer period of time it is possible to estimate the optimal stock size based on these records.

New stock should always be stored behind old stock, to make sure that the old stock is dispensed first. In the preparation and raw material monographs (chapters 12 and 13) an indication is given on the consequences of using expired materials and preparations. One should always try to comply with expiry dates. Expired preparations should preferably never be used, even in the likelihood that there are no risks associated with their use, and even if the shelf life given is quite arbitrary.

7.8 Safety precautions

Some of the raw materials that are ingredients for the preparations in this formulary, are highly active, toxic, irritating or staining. Raw materials requiring careful handling include coal tar, dithranol, gentian violet, lindane, iodine, potassium permanganate, phenol and silver nitrate. Contact of these raw materials with the skin and the eyes should be avoided while handling them, also during manufacturing. When available gloves can be worn. It is also advisable to wear safety goggles or one's own pair of spectacles. Clean up spoiled materials immediately. It is advisable to have someone else to control all calculations, weighings, and measurements of such materials. More specific information on the hazards of these materials is found in the raw material monographs in chapter 13.

7.9 Temperatures

Temperatures in this formulary are given in degrees Celsius (°C). In some countries degrees Fahrenheit are still being used. To calculate the temperature in degrees Fahrenheit when degrees Celsius are given, multiply by 9/5 and add 32 (formula 7-I). To calculate degrees Celsius when degrees Fahrenheit are given, subtract 32 and multiply the result by 5/9 (formula 7-II).

°F = °C x 9/5 + 32 formula 7-I
°C = (°F - 32) x 5/9 formula 7-II

Example 1:
You want to check the temperature of a solution with a thermometer having a Fahrenheit scale. The temperature should be 70 °C. The Fahrenheit scale should read 70 x 9/5 + 32 = 126 + 32 = 158 °F.

Example 2:
You measure a room temperature of 95 °F, but you want to know the temperature in degrees Celsius. This is (95 - 32) x 5/9 = 63 x 5/9 = 35 °C.

7.10 Weights and measures

In this formulary the SI international system of units is used. Weights are expressed in grams (g) and volumes in millilitres (ml) and the dot (.) is used to indicate the decimals in a number. Thus, for example 3.5 ml denotes the amount of three-and-a-half millilitre. To prevent mistakes, it is best to only use the SI unit system. However in countries where weights and measures in other unit systems are the only ones available, these can be used. All quantities of the preparations in this book then require calculation into the other unit system. Make sure that you know exactly how to do this and ask somebody to check your calculations in order to prevent errors.

In general percentages are given as w/w (weight/weight) for solids and semi-solids, and w/v (weight/volume) for a solid in a liquid. An exception is ethanol, of which dilutions are always prepared on a w/w basis. The reason for this is volume contraction. This means that the sum of a volume water added to a volume ethanol is always less than the sum of these volumes.

7.10.1 Volume units

The American system of volume units is based on the US gallon:

– 1 US gallon =				3785	ml (= 3.785 l)
– 1 US quart =	1/4	US gallon	=	946	ml
– 1 US pint =	1/8	US gallon	=	473	ml
– 1 US gill =	1/32	US gallon	=	118	ml
– 1 US fluid ounce =	1/128	US gallon	=	29.6	ml
– 1 US fluid dram =	1/8	US fluid ounce	=	3.7	ml
– 1 US minim =	1/60	US fluid dram	=	0.06	ml

Countries using the British system refer to the imperial gallon that is equivalent to 4546 ml. The corresponding values are:

– 1 imp. gallon =	4546	ml (= 4.546 l)
– 1 imp. quart =	1136	ml
– 1 imp. pint =	568	ml
– 1 imp. fluid ounce =	28.4	ml
– 1 imp. fluid dram =	3.55	ml

The other way around, the corresponding values for one millilitre are:

– 1 ml = 0.00026 US gallon = 0.0021 US pint = 0.034 US fluid ounce = 0.27 US fluid dram = 16.2 US minim.
– 1 ml = 0.00022 Imp. gallon = 0.0018 Imp. pints = 0.028 Imp. fluid ounce = 0.23 Imp. fluid dram = 13.5 Imp. minim

Check carefully whether volume units are in imperial or US gallons before calculating.

7.10.2 Weight units

Two unit systems for weights are still in use in some countries:

– 1 pound lbs (avoirdupois) =	454	g
– 1 ounce = 1/16 lbs =	28.4	g
– 1 draw = 1/16 ounce =	1.8	g
– 1 grain = 1/7000 lbs =	0.065	g

– 1 troy pound (apothecaries)			=	373	g
– 1 troy ounce =	1/12	troy pound	=	31.1	g
– 1 pennyweight =	1/20	troy ounce	=	1.6	g
– 1 grain =	1/5760	troy pound	=	0.065	g

The other way around, 1 gram is equivalent to:

– 1 g = 0.035 ounce (avoirdupois) = 0.564 draw = 15.4 grains.
– 1 g = 0.032 troy ounce (apothecaries) = 0.643 pennyweights = 15.4 grains.

The symbol for grain is gr, for gram g. Always use the right symbol for each of them to prevent mistakes. Be careful to check to which system pounds and ounces refer.

An example:
you want to measure 100 ml with a measure calibrated in fluid ounces (US):
100 ml = 100 x 0.034 = 3.4 US fluid ounces.

8 Basic pharmaceutical methods

8.1 Weighing

Measurements of solids are always done by weighing. Measuring a solid by volume is not accurate enough in drug manufacturing. Measurements of liquids, especially of larger amounts, are preferably also done by weighing for reasons of accuracy. Smaller quantities can be measured by volume which is easier but less accurate than weighing. Use formula 8-I to calculate the weight of a liquid for a given volume. Formula 8-II is used to calculate the volume of a given weight. The density is different for each liquid and depends on the temperature. For all fluid raw materials in this formulary reference density values at 20 °C are given in the monographs of chapter 13. These values are not valid for calculations when production conditions are at temperatures below 10 °C or above 30 °C.

weight	= density x volume	formula 8-I
volume	= weight / density	formula 8-II

8.1.1 General rules for weighing

For accurate weighing follow these rules.

- Use a balance that is suitable for weighing the required quantity. The minimal weight that is accurately measured with a balance is determined by multiplying the smallest scale unit by 200. Never try to weigh quantities exceeding the capacity of the balance. Check whether the balance and the weights are calibrated for the SI unit system. If not, use the conversion factors that are given in chapter 7.
- Before weighing, check that the balance is:
  - clean;
  - in a completely level position;
  - in a place free from draught;
  - set to zero or tarred.
- When using a non-electrical balance make sure the balance arm can move freely. This is checked by touching the balance pan with a forceps. Make sure the balance is in the down, or resting position, before transferring materials or weights to or from the pans.
- When using a non-electrical balance always use forceps to transfer weights; never touch weights with your fingers. Put weights back into the weight drawer or into their case immediately after use and close the weight drawer immediately. These procedures are to avoid corrosion and contamination of the weights and to keep them accurate.
- Never weigh pharmaceutical materials directly on the balance pan. Use a piece of paper for solids, waxed paper for semisolids, and an appropriate vessel for liquids. The vessel used for liquids requires cleaning after each weighing.
- Use a suitable spatula for the transfer of materials to the balance pan. Take care not to spill any material. Clean immediately after spilling material. The spatula should be cleaned after each weighing.
- Some pharmaceutical materials are corrosive or aggressive. Special containers and spatulas are sometimes needed. This is indicated in chapter 13 when relevant.

– After weighing a solid that has to be dissolved in a liquid, it can be washed off with that liquid.
– Clean the balance thoroughly after use.

8.1.2 Weighing with a double pan balance

1. Place a piece of paper, waxed paper or a suitable container on the right hand pan. Tare the balance by placing an equivalent piece of paper or container on the left hand pan. Weights or other tare equipment can also be used. Always use the right hand pan for the material that is to be weighed, and the left hand pan for the tares and weights.
2. Put weights equivalent to the required quantity on the left hand pan.
3. Transfer the material to be weighed to the right hand pan. Add enough material to balance the pans.

8.1.3 Weighing with a single pan balance

1. Set the balance to zero.
2. Place a piece of paper, waxed paper or a suitable container on the pan.
3. Read the scale and note the reading (X g). Always read the scale at eye level.
4. If Y g are to be weighed, add material until the scale reads X plus Y g.

Figure 8.1. Using a graded measuring cylinder: transferring a solution prior to making up to volume

8.2 Measurement of liquids

Liquids in smaller amounts are generally measured by volume, but can be measured by weighing as well (see paragraph 8.1). Measurement by volume is done with measures, pipettes, a dropper or syringes. The first method is used for larger volumes, the other ones for small volumes.

There is an essential difference between pipettes and other types of volumetric glassware, such as volumetric flasks. Pipettes are designed to deliver a certain volume, and they are used to transfer the required amount of liquid from one container to another. Volumetric flasks have an exactly known capacity. They are generally used to make a solution with a specified concentration. Graded cylinders (see figure 8.1) are frequently used for both purposes. When they are used to transfer liquids with high viscosity, a substantial amount may remain in the cylinder which leads to a relatively large measuring error.

8.2.1 Measurement with measures

For accurate measurements follow these general rules.

- Select a measure of a suitable size. Pharmaceutical measures show no scale lower than the minimum volume they are accurately used for.
- Make sure the scale of the measure is in millilitres (ml), not in centilitres, pints, gallons or any other unit. When a volume is stated in other units, use the conversion factors that are given in chapter 7.
- Always read the scale at eye level, at the bottom of the liquid surface (meniscus) as shown in figure 8.2. When reading the scale is difficult, hold a piece of dark coloured paper behind the measure.

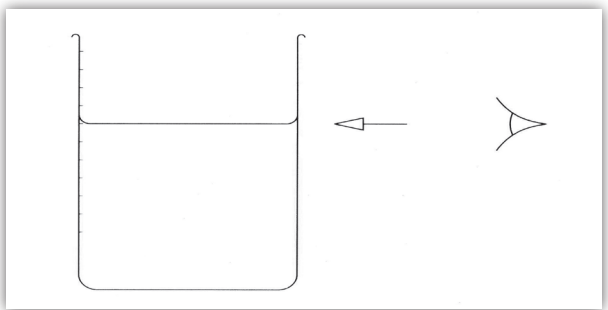

Figure 8.2. Reading the scale of volumetric glassware

- Make sure no liquid remains in the measure. It may take some time for the liquid to flow out completely, particularly when you are measuring viscous liquids. For water and aqueous solutions keep the measure top down for 15 seconds after all the liquid has flown out, and 2 minutes for syrups and oils.
- Measures should be cleaned and dried after each measurement. Measures should not be used while they are still wet.
- To prevent contamination of measures with dust, they should be kept upside down, preferably in a clean cupboard.

8.2.2 Measurement with pipettes

Pipettes are used for accurate measurements of small volumes. As an alternative, syringes can be used as well. Pipettes are calibrated for one specific liquid at one specific temperature. Usually this is water at 20 °C.

Pipettes can be used for the measurement of other liquids as well but are less accurate. It may be very difficult to clean the pipette after the measurement of oils.

For accurate measurements follow these general rules.
- Always use a pipette with a suitable volume.
- Make sure the scale is in millilitres (ml), not in centilitres, pints or other units.
- Read the scale at eye level at the bottom of the liquid surface (meniscus) as shown in figure 8.2. If you find it difficult to read the scale, hold a piece of dark coloured paper behind the scale.
- Liquid is drawn into the pipette through the application of a slight vacuum. A rubber suction bulb is preferably used to draw liquid into the pipette (left in figure 8.3). Mouth suction should never be used with dangerous or toxic liquids.

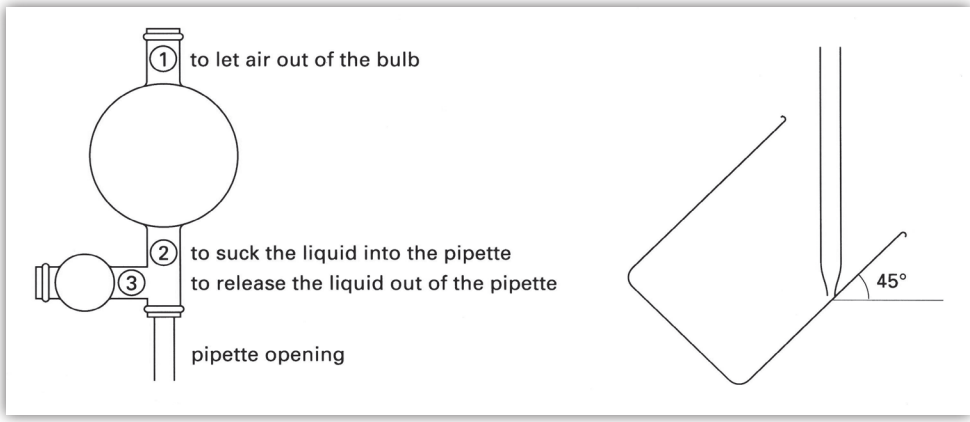

Figure 8.3. Using pipettes

Measurements with pipettes are done as follows.
1. Draw a small volume of the liquid to be measured into the pipette and thoroughly wet all the internal surface of the pipette. Allow the liquid to drain and discard it.
2. Carefully fill the pipette to a level slightly above the graduation mark.
3. Quickly replace the bulb (or mouth) with your forefinger to stop the liquid from flowing out. The best way to control the flow of liquid from the pipette is with a slightly wet forefinger.
4. Make sure there are no air bubbles in the fluid or on the fluid surface.
5. Wipe the outer surface of the pipette clean.
6. Hold the tip of the pipette against a glass vessel and allow the liquid to flow out until the bottom of the liquid surface just touches the graduation mark.
7. Place the tip of the pipette against the inner wall of the receiving container, holding the pipette in a vertical position and the container at an angle of about 45° from vertical, as shown at the right in figure 8.3. Allow the liquid to flow out by raising you fingertip.
8. When the free flow ceases, rest the tip against the wall of the container for an additional 15 seconds.
9. Rinse the pipette thoroughly after use.

8.2.3 Measurement with a dropper

A dropper is used to measure small quantities of a liquid. Any sort of apparatus that produces droplets of uniform size is appropriate for example Pasteur pipettes and droppers from eye drop bottles. The dropper needs calibration for the liquid that is to be measured with it. This means that the exact weight or volume per droplet is known (or the other way around, that the number of drops per g or ml is known).

Proceed as follows to calibrate a dropper. Fill the dropper with the liquid for which you are calibrating it. The apparatus should be clean and dry before filling. Count the number of drops needed to obtain a standard weight or volume that you can accurately measure (for example 1 g or 10 ml). Calculate the weight or volume per droplet with formula 8-III or 8-IV.

weight per droplet	= weight obtained / number of droplets	formula 8-III
volume per droplet	= measured volume / number of droplets	formula 8-IV

To measure a liquid with a dropper, fill it with the liquid requiring measurement. The dropper must be calibrated for that particular liquid. Calculate the number of drops that correspond to the required weight or volume with formula 8-V or 8-VI. Drop until the calculated number of drops is obtained. Clean and dry the apparatus immediately after use.

number of droplets	= weight required / weight per droplet	formula 8-V
number of droplets	= volume required / volume per droplet	formula 8-VI

8.3 Making up to volume or weight

8.3.1 Making up to volume

'Making up to volume' means adding a liquid vehicle to other ingredients to reach the required final volume. This is done in a measure of suitable size or in a calibrated vessel. All kinds of vessels can be used. To calibrate, fill the vessel with the required volume of water and mark the level on the outside. Use recently boiled and cooled water for calibration to prevent contamination of the vessel.

8.3.2 Making up to weight

Creams and ointments often require the addition of a vehicle or raw material to obtain the final weight, which is called 'making up to weight'. Weighing is generally done in the vessel in which the product is prepared provided the total weight of vessel, mixing device and product does not exceed the capacity of the balance. The empty weight of the vessel and mixing device should be determined and recorded before the preparation is started, to allow calculation of the total or final weight that is reached.

8.4 Size reduction and sieving of solids

Reduction of the particle size of solids is necessary when a fine powder is required and only crystals or a coarse powder are available. In dermatological preparations a particle size of less than 90 µm is preferred. Many raw materials already have a suitable particle size, but some do not and require size reduction. Some

materials require special precautions during grinding and sieving. Such special instructions are indicated in the preparation monographs in chapter 12 whenever necessary.

Grinding is done before mixing (dry grinding) or during mixing (wet grinding) with a liquid or semisolid. When sieving is necessary after particle size reduction, the only option is dry grinding. Raw materials are preferably grinded (and sometimes sieved) before the required quantity is weighed because some loss of material usually occurs during these procedures. Therefore make sure to start grinding and sieving with a small excess of the required quantity of the raw material.

8.4.1 Grinding before mixing

Place the solid material in a suitably sized stone mortar with a rough wall, and grind with a pestle. During grinding, use a suitable scraper from time to time to remove particles from the wall of the mortar. The material is preferably sieved after grinding.

8.4.2 Grinding during mixing

Place the solid material in a suitably sized stone mortar with a rough wall. Using a pestle, triturate this with an approximately equal amount of fluid or semisolid. 'To triturate' means to thoroughly rub between the wall of the mortar and the pestle to obtain a smooth and homogeneous mixture. Subsequently, stepwise add the remainder of the fluid or semisolid and mix. Remove the mixture from the wall of the mortar several times during grinding, using a suitable scraper. After wet grinding sieving is not possible. Smear a small amount of the mixture on a piece of glass or dark material to check for any remaining lumps.

8.4.3 Sieving

Sieves were formerly characterised by the number of meshes per inch, which was called the mesh number. Nowadays, the sieve number is used to characterise sieves. The sieve number indicates the nominal aperture size of the meshes in µm. Table 8.1 relates sieve numbers to mesh numbers. For dermatological preparations a particle size smaller than 180 µm is required but a particle size smaller than 90 µm is often preferred.

Table 8.1. Corresponding sieve and mesh numbers

Sieve number µm	*Mesh number /inch*
250	*60*
180	*85*
150	*100*
125	*120*
106	*150*
75	*200*

Sieving is used to separate fine powder from coarse powder or lumps. The powder is placed on a sieve with a suitable opening size. The material is gently stroked with a rubber stopper or other suitable equipment. A brush is sometimes advised, but brushes are very difficult to clean after use and may cause cross-contamination. The fine powder passing the sieve is collected in a suitable container or on a clean sheet of paper.

Mixtures always need remixing after sieving, as separation due to the sieving procedure occurs. Sieving is always done before weighing the required quantity.

8.5 Mixing ingredients

8.5.1 Mixing miscible liquids

Miscible liquids are easily mixed by shaking or stirring. Care should be taken not to introduce too much air.

8.5.2 Dissolving a solid in a liquid

A good and convenient procedure to prepare a solution is as follows. Weigh the required quantity of the solid in the vessel in which the solution is prepared, and add the liquid to this vessel bit by bit. Mix by stirring or shaking until dissolution is complete (see figure 8.4). Take care not to introduce too much air into the solution. Check for complete dissolution and homogeneity. This is very easy if the solution is prepared in a glass vessel. If the solid is added to the liquid, check that all solid material is transferred into the container. In certain cases gentle heat (see paragraph 8.6) is applied to speed up the dissolution process. However, gentle heat cannot be used to increase the solubility because crystallisation occurs again upon cooling. Also, gentle heat is inappropriate when the solid or liquid is unstable. The application of gentle heat during manufacturing is indicated in the preparation monographs in chapter 12.

8.5.3 Mixing solids

Mixing solids is preferably done in a stone mortar with a rough wall, by carefully rubbing the solids together between the pestle and the wall of the mortar. This is called trituration (see also paragraph 8.4.2 where trituration of a solid and a liquid is described). Use a mortar of a suitable size for optimal mixing efficiency and minimal spoilage risk. The mixing process is most efficient when approximately equal amounts of solids are mixed. If a relatively small amount of a solid A requires mixing with a large amount of solid B, this is done most efficiently by first mixing A with an equal amount of B. The remaining part of B is added gradually in portions that are approximately equal to the amount already in the mortar. During mixing, use a suitable scraper to remove particles from the wall of the mortar from time to time.

A mixture of solids gets inhomogeneous during transport or sieving. If you have any doubts concerning the homogeneity of a powder mixture, re-homogenise it by mixing in a mortar before use.

8.5.4 Mixing a solid with a semisolid

Mixing a solid with a semisolid ointment base is a common pharmaceutical operation. It is preferably done in a mortar. The solid is first triturated with an equal part of the semisolid, because equal parts mix best. Triturating is thoroughly rubbing the ingredients between the pestle and the mortar wall to obtain a smooth and homogeneous mixture. The remainder of the semisolid is added gradually. During mixing, from time to time remove particles from the wall of the mortar with a suitable scraper. Use a mortar of suitable size for optimal mixing efficiency and minimal spoilage risk.

Figure 8.4. Mixing in practice: stirring by hand

In rare cases, the application of gentle heat is required to ensure efficient mixing. Such cases are indicated in the preparation monographs in chapter 12.

8.5.5 Mixing fatty substances

Fatty substances are usually mixed by melting them together over gentle heat (see paragraph 8.6) in a metallic mortar with a plastic pestle. The melted material is stirred until homogeneous, and gentle stirring is continued until the mixture has cooled down. Semisolid materials are sometimes mixed without melting.

8.5.6 Mixing a liquid and a semisolid

Mixing a liquid and a semisolid is usually done without melting. The liquid is added to the semisolid by small quantities at a time. Mix well after each addition.

8.6 Heating

The application of heat is often required. Two types of heat are distinguished, heat and gentle heat. Heat is primarily used for boiling water. Any heat source like gas, petroleum, wood, coal, electricity etc., is used for this purpose. Gentle heat is used for melting fatty substances and speeding up dissolution. The above mentioned heat sources are unsuitable when gentle heat is required, because they produce so much heat that there is a great risk of overheating the material. For gentle heat a water bath is most suitable. On a water

Figure 8.5. Heating in practice: using the gentle heat of a water bath

bath the material is heated indirectly by hot water. Overheating is prevented because water cannot reach a temperature higher than 100 °C. Simple pans filled with water are suitable as a water bath (see figure 8.5). It is also convenient to put the lid upside down on the pan; this produces a warm surface on which materials are heated gently.

8.7 Sterilisation

Heat is also used to sterilise solutions. Sterilisation reduces the number of micro-organisms in solutions, which is required for solutions that are used for example on open wounds. To sterilise solutions they have to be kept at a temperature of 121 °C for at least 15 minutes. This is only possible under higher pressure. Sterilisation is usually done in an autoclave with adequate facilities to check both the temperature and the pressure. When autoclaves are unavailable, a pressure cooker is used provided it has a facility to check the temperature and/or the pressure.

Proceed as follows to sterilise containers with a solution.

1. Fill the autoclave or pressure cooker with sufficient water. A minimum water level should be maintained throughout the sterilisation procedure.
2. Bring the solutions requiring sterilisation into the autoclave or pressure cooker. The solutions are packed in their final containers. The container must be able to resist a temperature of 121 °C. Glass is very suitable. If the container is able to resist high pressure, close it tightly. If the packaging is not able to resist high pressure (e.g., glass containers), the closure should be loosely fitted to allow pressure adjustments during the sterilisation process.
3. Close the autoclave or pressure cooker.
4. Open the steam valve.
5. Heat until the water boils. The temperature then is 100 °C and the autoclave or pressure cooker is steaming.
6. Allow to steam for 10 minutes and then close the steam valve. The pressure rises to 2 bar (approx. 2 atmosphere) and the temperature rises to 121 °C.
7. Maintain the autoclave or pressure cooker at this pressure and temperature for 15 minutes.
8. Switch off the heat source and allow to cool to 80 °C. Open the steam valve, then open the autoclave or pressure cooker, if present close the containers that could not resist high pressure and were sterilised with loosely fitted closures, and take the sterilised solutions out.
9. Label or mark the containers clearly as being sterilised.

9 Stability of dermatological preparations in the tropics

This chapter deals with the stability of raw materials and preparations. Pharmaceutical preparations require a good quality immediately after manufacturing, as well as during the period when patients use them. Therefore, the quality that is achieved during production must be maintained; in other words, the product must be sufficiently stable. The chapter starts with a general introduction on pharmaceutical stability and shelf life, then takes a somewhat deeper look into chemical stability, and proposes some general ideas on how to optimise shelf life. It continues to discuss some details on the stability of a number of raw materials that are of specific interest to this formulary. The chapter ends (paragraph 9.9) with a summary of relevant stability details of the raw materials for quick reference.

9.1 General introduction on stability

The quality of a dermatological – or any pharmaceutical – product matters most at the time of use. Hence the product must be of good quality immediately after production and needs to keep this quality over a given period, i.e., the shelf life. Therefore, a reasonably stable product has to be prepared and the period in which it retains its quality needs to be known.

Stability is a relative concept. In time and in extreme conditions all materials and products deteriorate, but some perish faster than others. Given the tropical climate conditions of many developing regions and countries, we considered stability an important aspect of the choices for this formulary. Despite this, we were not always able to choose products with sufficient stability over a longer period of time.

When stability is an issue, there are three ways to deal with it. The first is to set a short shelf life, or to allow the product's use only immediately after preparation. The second way is to improve the formulation of the product, either by choosing the optimal composition or preparation method. The third is to control the storage conditions to improve stability and shelf life. This is for example done by protective packaging, regulating and controlling temperature or humidity, or by preventing exposure to (sun)light. The best way is to consider these options in connection to each other, keeping in mind the resource scarce context in which the preparations are produced and used. A short shelf life is often impractical or even impossible in specific circumstances, and managing storage conditions may prove difficult, especially after dispensing the dermatological preparation to the patient.

A pharmaceutical preparation deteriorates due to chemical reactions, physical processes, or from microbial growth and decay. These processes are very different, as well as the conditions promoting them. In this chapter we therefore differentiate between chemical stability, physical stability and microbial stability. All three processes contribute to the shelf life of raw materials and the products made from them. Information on the shelf life of dermatological preparations that is found in references and scientific literature is generally not applicable to producing, storing and using such preparations in tropical conditions. This chapter provides background information on the general principles determining the actual shelf life of dermatological

preparations. These principles, together with knowledge about the shelf life of materials and preparations in temperate climate conditions, were applied to calculate the shelf life of the preparations in tropical conditions and advise on storage conditions. This information is given in chapter 12 regarding the dermatological preparations, and in chapter 13 for the raw materials.

9.1.1 Definitions

Most deterioration processes are irreversible which means that an affected or spoiled product cannot be restored. Some processes are reversible and in these cases it is possible to recondition the product. This can be simple, for example by stirring an ointment to homogenise it again, but can also be much more complex. For products included in this formulary the practical examples of reversible deterioration mostly relate to the physical processes of sedimentation and melting.

Deterioration can occur at three stages in the life time of a dermatological product, i.e., during storage of the raw materials before preparation, during storage of stock after preparation, and after dispensing when it is being used by the patient. It is therefore relevant to distinguish between the shelf life for:

- Raw materials, indicated by: DO NOT PROCESS PAST dd/mm/yyyy;
- Stock preparations, indicated by: DO NOT DISPENSE PAST dd/mm/yyyy;
- Preparation used by the patient, indicated by: DO NOT USE PAST dd/mm/yyyy.

In addition, there may be therapeutic or safety reasons to set a maximum period for using a product. Such information is provided in the monographs.

To determine the shelf life of a dermatological preparation, the degradation processes, local conditions, and quality criteria need to be taken into account. Shelf life is usually defined as the time during which the preparation complies with the pharmacopoeia standards. A practical, but arbitrary, limit is that at least 90% of the declared quantity of active ingredient, the drug, should be present in the preparation. In certain specific cases a wider limit is acceptable, or the shelf life can be prolonged by adding an excess of the active ingredient. In addition to the activity of the preparation, the toxicity of degradation products also needs to be considered when determining the shelf life. When toxic degradation products are formed, their no-effect level dictates shelf life. Carcinogens may not be present at any time, because their no-effect level is zero.

9.1.2 Chemical stability

Different types of chemical reactions are involved in chemical stability. Each reaction is influenced by different conditions and is therefore limited by different preventive measures. High temperatures speed up most chemical reactions that generally limit the stability of products (see paragraph 9.1.3).

Hydrolysis and oxidation are by far the most common degradation reactions limiting the shelf life of a material or preparation.

a. Hydrolysis is a reaction that breaks a molecular bond in the presence of water. The presence of an acid or a base usually speeds up (catalyses) this degradation reaction. Keeping the material dry and carefully choosing the pH at which the highest stability is achieved are possible preventive measures.
b. Oxidation is defined as electron loss. As the name implies it often involves oxygen. If oxygen is involved a fully filled airtight container helps preventing a product from being oxidised. Another preventive measure

is the addition of an antioxidant. The antioxidant is easier to oxidise than the main ingredient requiring protection. The antioxidant uses all available reactant (oxygen) leaving nothing to oxidise the main ingredient. Oxidation reactions are often catalysed by heavy metal ions. These can be taken away using complex forming agents such as disodium edetate.

c. Photochemical reactions occur under the influence of light. They are prevented by storage in the dark, or in dark containers.
d. Isomerisation reactions influence the potency and safety of the active ingredient. Isomerisation is the process by which an optically active molecule changes into its mirror image or isomer. Different isomers may exert different biological properties.
e. Some active ingredients are inactivated by polymerisation reactions. Such reactions are characterised by molecules forming bonds between each other to form larger molecules.

9.1.3 Chemical reaction kinetics

The above mentioned chemical degradation reactions result in reduced concentrations of the active ingredient(s) and ultimately inactivation of a preparation. It is important to know, or at least estimate the degradation rate to determine the shelf life of a raw material or preparation. Chemical reaction kinetics is the study of the rate of chemical reactions. It deals with the experimental determination of reaction rates from which rate laws and rate equations are derived.

Many factors affect the reaction rate:

- Nature of the reactants and the mechanism of the reaction.
- Physical state (solid, liquid, gas), particle size and surface area.
- Concentration. According to the collision theory molecules must first collide in order to react with each other. At higher concentration – it is more crowded – molecules collide more often and reaction rate increases.
- Temperature. At higher temperatures molecules have more energy and react more easily. As a very rough rule of thumb the reaction rate often doubles for every 10 °C temperature rise.
- Catalysts. A catalyst is a substance that does not take part in the chemical reactions itself, but speeds it up.
- Pressure.

The relationship between concentration and time is characterised by two parameters: the order of the reaction and the reaction rate constant. The order of the reaction describes the shape of the concentration-time curve (see figure 9.1), the reaction constant defines the slope of the curve. The chemical reaction is described by general formula 9-I, and the reaction rate by formula 9-II. Together they determine the order of the reaction as expressed by formula 9-III.

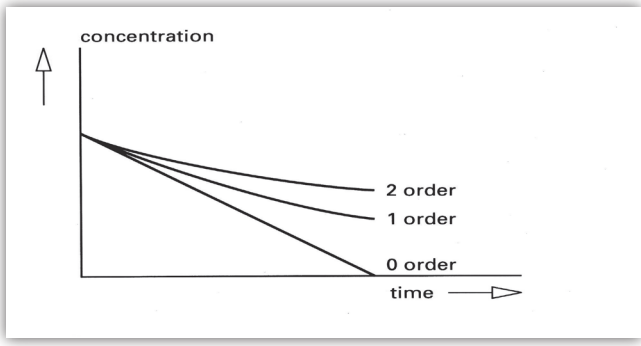

Figure 9.1. The relation between concentration and time (the concentration-time curve) for zero-, first- and second order reactions

$aA + bB \rightarrow cC + dD$

$v = k[A]^a . [B]^b$ formula 9-I

$n = a + b$ formula 9-II

formula 9-III

A, B	=	reactants
a, b	=	number of molecules of A and B reacting
C, D	=	products
c, d	=	number of molecules of C and D formed
[A]	=	concentration of reactant A
v	=	reaction rate
k	=	reaction rate constant
n	=	order of reaction

If a reaction has a single reactant and the value of the exponent n is one, it is a first order reaction. In this case the concentration of the reactant decreases while the reaction takes place and the reaction rate decreases at the same time, as the reaction rate is directly proportional to the concentration. Many reactions involve more than one reactant and therefore have a higher theoretical order of reaction that is mathematically determined. For such reactions the reaction rate equations are more complex.

In chemical reaction kinetics the reaction rates and the order of reaction are experimentally determined. Very often the observed order of the reaction differs from the theoretical order of the reaction. The observed order of reaction is generally called pseudo reaction order. The theoretical and observed order of reactions are most often different when the reaction rate is dependent on a single rate-determining step or process. In actual practice, many reactions are adequately described by pseudo first order, or by pseudo zero order kinetics. In pseudo zero order reactions the reaction rate does not change with the concentration and therefore is constant over time. This is for example the case when dissolution of the reactant is the rate-determining step.

The reaction rate constant determines the slope of the concentration-time curve. When the order of the reaction and the reaction rate constant are known, the degradation in a given time can be calculated. The following formulae are used, formula 9-IV for zero order reactions, and formula 9-V for first order reactions:

$$k = \frac{[A]_0 - [A]_t}{t}$$ formula 9-IV

$$k = \frac{\ln [A]_0 / [A]_t}{t}$$ formula 9-V

k = reaction rate constant
[A]o = original concentration
[A]t = concentration remaining
t = time

In industry, the shelf life of drugs is usually calculated from data obtained at slightly higher temperatures than the generally expected storage temperatures (also taking into account any other relevant chemical, physical or microbial processes). It is possible to calculate the reaction rate constant at a different temperature with the Arrhenius equation (formula 9-VI).

$$k = A.e^{-Ea / R.T}$$ formula 9-VI

k = reaction rate constant
Ea = activation energy
R = 8.314 J/mol.K
T = absolute temperature (K)
A = frequency factor

A and Ea are approximately constant over a limited temperature range. If these values are known, or if the reaction rate constants at two temperatures are known, the reaction rate constant at a given temperature can be calculated.
In many cases a number of consecutive reactions are involved in degradation, and the only reaction parameters known are those of the overall reaction. These are called "observed" or "apparent" reaction rate constants (1).

9.1.4 Chemical stability: temperature

Raw materials and dermatological preparations generally have a shorter shelf life in tropical climates compared to moderate climate zones. To calculate or estimate the shelf life in tropical climates, information is required on the shelf life in moderate conditions and a method to account for temperature differences and their effects.

To differentiate between countries with different temperatures, various climate zones are defined (1). They are usually classified as follows:

I : Temperate zones.
II : Mediterranean and subtropical zones.
III : Hot and dry zones.
IV : Hot and humid zones.

Degradation due to chemical reactions is dependent on the temperature. Since the relation between reaction rate and temperature is complex, it is difficult to determine how the temperature affects the shelf life in tropical climate conditions. Haynes introduced the method to calculate with kinetic average temperatures, which are also known as virtual temperatures. The concept of the kinetic average temperature is explained in this paragraph.

In circumstances without temperature control the temperature changes constantly, and reaction rates of degradation reactions in preparations also change constantly. This applies for example to tropical climates where the extremes in temperatures differ largely. A shelf life calculated with the highest extreme

temperature, to be on the safe side, is very short. On the other hand, if it is calculated on a simple average temperature it may underestimate the degradation effects of the highest temperatures and turn out to be unsafe from a therapeutic point of view. Calculating with the kinetic average temperature aims at taking into account the actual differences and effects under changing circumstances. Therefore, the degradation rates at the kinetic average temperature are the same as the degradation rates at the complex pattern of temperatures occurring in reality (2,3). The concept allows for reaction rate estimations for complex and varying temperature patterns as they are encountered in actual practice.

The concept of the kinetic average temperature has received very little scientific attention during the past decades. In the developed world, the general approach is to determine a reasonable shelf life at a practical temperature and to control the actual storage temperature of the product. A typical Dutch community pharmacy for example is able to maintain, monitor and guarantee product storage temperatures at -20 °C, 2-8 °C, and 15-25 °C. In such circumstances calculations at actual, non-controlled temperatures are not relevant. But the medicine storage conditions in resource scarce areas that are the focus of this book, are very different and do require a method to estimate degradation rates under varying, non-controlled, conditions. As to our knowledge the concept of the kinetic average temperature has never been discredited we decided to use it for our shelf life estimates.

Kinetic average temperatures are dependent on activation energy constants, which are characteristic for drugs. Therefore, theoretically, the kinetic average temperature is also characteristic for a specific drug. Haynes calculated that the maximum error in kinetic average temperatures due to differences in activation energy between drugs was only 1 °C (2). This error is negligible and thus allows calculations with the same activation energy constant as well as the same kinetic average temperature for many drugs.

In most climates the temperature pattern fluctuates; there are hotter and cooler periods. If a drug can only be stored for a short period of time, it is best to stay on the safe side and to estimate the shelf life for unstable drugs and preparations using the temperatures of the hottest period of the year. For drugs that can be stored for at least a year, a yearly average can be taken. Grimm calculated kinetic average temperatures for climate zones III and IV at different times of the year. During the eight months with the lowest temperatures, the kinetic average temperature was 27 °C, during three hot months it was 34 °C, and during the hottest month it was 40 °C. Over one full year the kinetic average temperature was 31 °C. This was raised to 33.6 °C after transport under extreme circumstances or to 32.4 °C over two years after transport. These values are calculated assuming that the activation energy is 20 kcal/mol; for chemicals with high activation energy of 30 kcal/mol the error is only 0.5 °C. Grimm's calculations are based on extremes and are considered safe for worldwide use (3). This means that for climate zones III or IV and a shelf life of less than 3 months, shelf life calculations are done for 40 °C. A shelf life of more than 3 months is calculated for 34 °C.

These kinetic average temperatures are used in the Arrhenius equation (formula 9-VI) to calculate the reaction rate constant for a specific degradation reaction. The reaction rate constant of the fastest degradation reaction is then used with the appropriate reaction rate equation to calculate the shelf life. The appropriate reaction rate equation depends on the order of the reaction, for an (apparent) zero order reaction formula 9-IV is used, for an (apparent) first order reaction formula 9-V. For higher orders of reaction the formulae are more complicated.

If no toxic degradation products are formed, a 10% level of degradation products is generally accepted. This is equal to a level of 90% of the original product. Therefore a degradation of 10% means that, stated as

percentages, $[A]_0$ is 100 and $[A]_t$ is 90. If toxic or harmful degradation products are formed their no-effect level dictates how much degradation is acceptable. This is calculated with the relevant reaction equation.

The kinetic average temperature is a concept based on chemical reaction kinetics, and its use is limited to calculations of chemical stability. It should not be applied to physical or microbiological processes and stability.

9.1.5 Physical stability

A wide variety of physical processes affects the quality of stored raw materials and preparations. Adequate packaging is crucial to limit the loss of ingredients due to physical deterioration processes. Issues most likely to be encountered are:

a. Evaporation. This depends on many parameters. Temperature and air movements ('wind') are the most important environmental factors. Evaporation is a reversible process. In a well filled, airtight container it only leads to minimal loss of ingredients. Evaporation losses occur from containers that cannot be closed airtight or are permeable for gases.
b. Melting. Like evaporation, melting is in most cases a reversible process. If the preparation is adequately packed, it will not result in a loss of ingredients. Materials with a melting point below 70 °C should never be packed in paper or plastic bags. After resolidification the particle sizes are different and polymorphic changes occur.
c. Congelation or thickening. This occurs at low temperatures and is unlikely to pose a problem in tropical climates. It is a reversible process; solid materials are melted by warming them gently.
d. Crystallisation. This occurs at lower temperatures. Storage in a refrigerator can elicit crystallisation. When it happens, gently heating the material reverses crystallisation. If crystallisation is expected, the product or raw material requires gentle heating and mixing before use.
e. Hygroscopicity, or absorption of moisture from the environment. This is a serious issue as secondary processes may lead to a loss of ingredients or material. Such secondary processes include microbial spoilage and chemical degradation, especially hydrolysis. For some materials dissolution in absorbed water is possible. Subsequent processing of the material is difficult. It is very difficult to prevent absorption of moisture. The materials should be kept in airtight containers at all times.
f. Sedimentation of lotions (suspensions or emulsions). In many cases this is a reversible process. Shaking or stirring results in proper re-suspension or re-emulsification if the product is of good quality. In some cases the sediment becomes so compacted that it is no longer possible to obtain a proper suspension by shaking or stirring. This is called caking. When this happens the product must be discarded. The formulation of a pharmaceutical product should prevent caking as much as possible, and the packaging should allow either stirring of shaking the lotion and visually checking its homogeneity. Sedimentation causes differences in concentrations of the active ingredient between the top and bottom layers, which may cause therapy failures or increased risks of side effects. This is a relevant issue for lotions containing benzyl benzoate.
g. Separation. Emulsions may separate into oily and aqueous layers. This process is called cracking. It is facilitated by sedimentation, which in this case is called creaming. Thickening agents are added to prevent creaming, and adding a suitable emulsifier prevents cracking. Many, but not all, emulsions are restored by stirring or shaking. Again, the packaging should allow stirring or shaking and a visual check on homogeneity.
h. Separation by squeezing out liquid. This happens to gels and is sometimes called bleeding. In most cases the process is reversible by stirring. Semi-solid gel preparations are therefore preferably stored and dispensed in jars with wide openings.

Many creams and ointments are semi-solid suspensions in which the active ingredient is suspended. Such products are vulnerable to sedimentation and phase separation. This poses a special issue as sedimentation is not easily visible. Therefore, preparations that are particularly at risk require stirring before application to the skin. They should be dispensed in jars with wide openings.

9.1.6 Microbial stability

Micro-organisms spoil a preparation when they are present in sufficient numbers. Preventing micro-organisms from getting into the preparation and preventing their growth are necessary precautions. Micro-organisms have two routes to get into a preparation; either they are already present in contaminated raw materials, or they get in during preparation or use.

Some raw materials contain large numbers of micro-organisms due to either preparation methods or provenance of the material. In the absence of water some organisms are able to remain viable for long periods of time. This is not limited to spore forming organisms. When the environment is favourable, micro-organisms grow and eventually spoil the material. This can be secondary to absorption of moisture from the air, as was shown for starch (4). Dry storage of raw materials in airtight containers helps to prevent this. Bentonite can be heavily contaminated with micro-organisms due to its production method. Water can also be heavily contaminated. Therefore, all water used for the preparation of dermatologicals requires boiling immediately before use. The Appendix informs on how to obtain clean and microbiologically safe water.

Hygiene is of prime importance. The Good Manufacturing Practicing (GMP) rules for hygiene (see chapter 6) need to be adhered to by all pharmacy personnel. This is important during both preparation and dispensing activities. Contamination by the patient or user of the product is also of concern. To prevent this, patient education is useful but generally has limited effects. Clever packaging may be more helpful. Collapsible tubes have become the major packaging material for semi-solid dermatologicals worldwide, because they prevent contamination of the preparation. However, they also have major drawbacks in tropical regions, as visible inspection and stirring or mixing are impossible.

Complete absence of microbial contamination is very difficult to obtain especially in resource scarce circumstances. Therefore a focus on growth prevention is required. The following aspects of a preparation's composition are relevant regarding microbial growth:

a. Micro-organisms need water to grow. They are able to survive in the absence of water, but do not grow. Microbial spoilage is unlikely to occur when no water is present.
b. Some raw materials or product characteristics exert antimicrobial effects. Propylene glycol (15%), glycerol (30%), ethanol (15%), high concentrations of sugars, high acidity or alkalinity prevent microbial growth.
c. Preparations containing water are usually preserved. Preservatives such as parabens or sorbic acid kill growing micro-organisms. Sometimes an active ingredient also has a preservative effect, e.g., phenol in calamine lotion.

9.1.7 Packaging and stability

Packaging materials and packaging design play a crucial role in maintaining product and drug stability. First, the packaging should protect the preparation from adverse environmental conditions. For chemical stability

protection against humidity, oxygen and light are most important. For physical stability protection against water vapour and gas permeability are important, as well as the integrity of the packaging or container. For microbial stability the integrity of the packaging or container is also most important. From a microbial point of view the collapsible tube has important advantages because it prevents contamination during use.

In addition to protection, other requirements for packaging are also important in tropical climates. The ideal packaging allows visual inspection of the contents. Also it should facilitate remixing the preparation by stirring or shaking. In practice these are often opposite requirements. A dark coloured bottle protects from light but hinders visual inspection. And a collapsible tube protects from microbial contamination but makes stirring virtually impossible. The optimal packaging is therefore always a compromise.

9.1.8 Packaging materials

To protect a substance adequately, the packaging material has to be chosen carefully. Other relevant characteristics of packaging materials include:

- Weight of the material because this is a major determining factor in transport costs.
- Cost of the materials and the container production.
- The possibility to re-use the container or packaging.
- Environmental hazards due to discarded packaging materials.

The costs for purchasing containers and their reusability are related issues requiring assessment taking into account the local possibilities. A deposit system could be considered. Table 9.1 summarises the properties of some container materials.

Table 9.1. Properties of various packaging materials

Material	*Impermeability for water vapour*	*Impermeability for oxygen*	*Low weight*	*Low cost*	*Reusability*
Paper	*very poor*	*very poor*	*excellent*	*excellent*	*poor*
Glass	*excellent*	*excellent*	*poor*	*good*	*excellent*
Polyethylene	*variable**	*variable**	*good*	*good*	*good*
PVC	*variable**	*variable**	*good*	*good*	*good*

* The outcome differs according to the quality and additives in the material

9.1.9 Packaging design

A keen container and cover design are equally important as the choice of the material they are made from. The packaging design should preserve the product's stability and facilitate a number of practicalities. Comparable to finding the most suitable material, packaging design is always a compromise. If the ideal format is not feasible, choosing preparations that are stable enough for dispensing in suboptimal packaging is another option. In the formulary we tried to optimise the preparations from this perspective.

Preparations that tend to become inhomogeneous require stirring before dispensing and use. A container with a wide opening is ideal for such products. A wide opening is also essential to allow cleaning the containers for re-use. On the other hand, a wide opening increases the risk for microbial contamination, and

so does frequent stirring. Collapsible tubes are not appropriate as they do not allow checking homogeneity of the product or stirring.

The storage space for empty containers and the weight of containers are important aspects in terms of transport costs. Conical containers could be designed which are easily stacked without a cover on top. Also, conical containers with a wide opening are easy to clean.

Covers should be designed to fit tightly, but should not be too difficult to open. Furthermore, to allow re-use, it should be possible to open and close the packaging many times.

Suitable packaging materials for dermatological preparations include:
- Coloured glass bottles for fluid preparations.
- Polyethylene jars of conical shape with a wide opening for semi-solids. Glass can be used instead, but this is somewhat more expensive and heavier.
- Glass jars for a limited number of semi-solid preparations that cannot be packed in the polyethylene jars (e.g., zinc oil and dithranol preparations).

9.1.10 Storage conditions and stock management

The stability and shelf life of products are also affected by storage conditions and proper stock management. In resource scarce regions many conditions can be influenced to some extent, and proper stock management helps to create the most favourable conditions.

The climate, heat and humidity cannot be influenced. However, inside temperatures depend on the building design. Local builders in tropical countries often know how to prevent excess heat by clever building design, for example keen roof work and ventilation. Protection from light is often possible for example by storing packaged preparations in boxes. A high humidity is partly prevented by repairing leaks promptly and remedied by proper ventilation. Ventilation, however, often brings hot air inside, so it should be done cleverly. Local people are likely to be experts on such matters.

Stock management requires an orderly set up administration. This helps to reduce the excess amounts of stock preparations which are likely to expire. It also helps to prevent shortages. Keeping an up-to-date stock register with expiry dates helps to ensure that expired stock is discarded. Stocks should always be organised by the FIFO principle: First In, First Out. This means that new stock is put behind older stock, so that the older stock is dispensed first. This prevents unnecessary loss due to expiration.

9.2 Hydrolysis of benzoic acid esters

9.2.1 Introduction

Benzoic acid esters are often used in dermatological preparations. The compounds relevant to this book are the preservative methylparaben and the scabicide benzyl benzoate.

9.2.2 Reaction mechanism

The hydrolysis of benzoic acid esters (see figure 9.2) involves various mechanisms, depending on the reaction medium and the substituents on the ester group and the benzene ring. Hydrolysis is acid

or base catalysed. The reaction mechanism depends mainly on the ester substituent, the benzene substituent only influences the reaction kinetics to some extent, but not the mechanism.

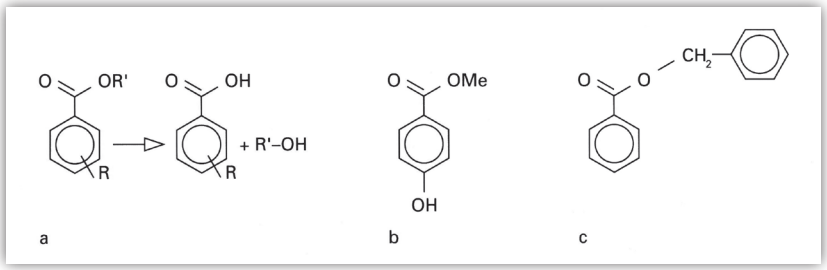

Figure 9.2. Hydrolysis of benzoic acid esters (a); molecular formula of methylparaben (b) and of benzyl benzoate (c)

9.2.3 Stability of the parabens

Parabens are hydroxybenzoic acid esters which are degraded by hydrolysis. This yields an alcohol (methanol, ethanol, or propanol) and hydroxybenzoic acid. These products are relatively non-toxic. The main drawback of the hydrolysis of parabens is reduced activity. Various authors determined the reaction kinetics at different pH values and temperatures. The hydrolysis reaction is strongly dependent on the pH (12).

Methylparaben is reasonably stable at pH values between 3 and 6. The reaction parameters for propyl- or ethylparaben are comparable to those of methylparaben. Basic cream is slightly acidic and methylparaben is stable in this preparation. Because methylparaben has a good activity in basic cream and is generally well tolerated, it is an appropriate preservative for basic cream. The parabens are even more stable when avoiding contact with water. When properly packed, the raw materials can be stored for longer periods of time (several years). Parabens are unsuitable preservatives for shake lotions with an alkaline pH, such as calamine lotion.

9.2.4 Stability of benzyl benzoate

Benzyl benzoate degrades to benzoic acid and benzyl alcohol. These degradation products are less active against scabies mites. They are relatively non-toxic and act as preservatives in the lotion. Baker and co-workers found low contents of benzyl benzoate in some emulsions (formulated according to the *British Pharmacopoeia*) but only small amounts of the degradation products. They assumed that the low concentrations of benzyl benzoate did not result from degradation, but from partial separation of the emulsion at the time of dispensing (13). Benzyl benzoate emulsion should always be well mixed before dispensing and before application. Hydrolysis of benzyl benzoate in emulsions is expected but is limited as there is little contact with water. The only possible contact of benzyl benzoate is at the interface of the oil and aqueous phases, because benzyl benzoate is not dissolved in the water but in the oil phase. The emulsion is therefore suitable for storage during longer periods of times. However, for reasons of physical and microbial stability, we recommend to use benzyl benzoate emulsion within 3 months after production. The raw material is stable when contact with water is avoided.

9.3 Stability of chlorhexidine in solutions

9.3.1 Introduction

Chlorhexidine solutions are widely used throughout the world as an antiseptic. Hydrolysis of the compound is expected. Chlorhexidine is usually marketed and stored in stock solutions. It is therefore important to know if, and if so, how fast the hydrolysis occurs.

9.3.2 Degradation products

Chlorhexidine degrades by hydrolysis. Various anilines are formed. One of the major degradation products is parachloraniline (see figure 9.3). Chloranilines are toxic substances which are absorbed through the skin. In higher doses chloraniline induces methaemoglobinaemia and other toxic effects (16). These toxic reactions are unlikely to occur after applying chlorhexidine solution to the skin. Chloranilines are associated with cancer, but the issue remains unclear. Although suspected carcinogens should not be present in any compound used for the preparation of drugs, it is impossible to determine a no-effect level for this class of toxic substances. The U.S. Pharmacopeial Convention (USP) limits the level of parachloraniline in chlorhexidine mouthwash to less than 3 ppm (17).

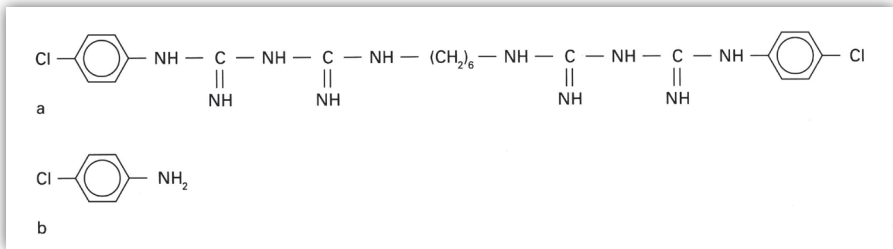

Figure 9.3. Hydrolysis of chlorhexidine (chlorhexidine: a, parachloraniline: b)

9.3.3 Reaction kinetics

Chlorhexidine is most stable at pH values between 5 and 6, and hydrolysis increases at higher or lower pH values (17). Degradation of chlorhexidine due to sterilisation is appreciable; chloraniline contents after sterilisation usually exceed the *British Pharmacopoeia* limit of 500 ppm (15). In the literature various reaction parameters were reported, both at sterilisation temperatures (14,15,18), at ambient temperatures (3,14,19-21) and at 90 °C (17). Degradation was accelerated by light (21). It is very difficult to use these parameters for an accurate calculation of the shelf life of chlorhexidine solutions, but it is reasonable to assume that their stability in tropical climates is a potential issue.

9.3.4 Choosing the chlorhexidine form

Chlorhexidine is most stable when it is kept free from water. Chlorhexidine digluconate cannot be kept free from water, because it is only available as a solution. The diacetate salt is available as crystals. As the raw material is expected to be kept in stock for longer periods than the preparations made from it, in the case of chlorhexidine the stability of the raw material is more critical than that of the preparations. Chlorhexidine diacetate crystals have a far better stability than the chlorhexidine digluconate solution. Chlorhexidine diacetate is as active as chlorhexidine digluconate, but its solubility in water is less (1.5% w/v). This is just high enough to prepare chlorhexidine solutions of the required strength, i.e., 1% w/v. The diacetate form is not

as widely used as the digluconate form. The choice which form to use must be made locally, considering the required storage times, local storage conditions and availability.

9.4 Stability and formulation of dithranol

9.4.1 Introduction

Dithranol is a highly reactive substance and therefore it is unstable. Various components of the vehicles that are generally used affect the stability of dithranol. These relative incompatibilities require special precautions to formulate dithranol, such as the addition of stabilisers. This is particularly important for tropical regions.

9.4.2 Reaction mechanism

The degradation reaction of dithranol is oxidative. Free oxygen radical mechanisms play a role. Radical initiators catalyse degradation reactions. The reaction leads to 1.8-dihydroxyanthraquinone and 1.8.1′.8′-tetrahydroxydianthron (see figure 9.4). The other hydroxy groups are also attacked. This results in polymerisation products (22,23). It is uncertain whether degradation products contribute to dithranol's therapeutic activity or side effects. Some degradation products are biologically active. For example anthralin brown influences the activity of glucose-6-phosphate-dehydrogenase (24). It is difficult to assess the risks that are associated with using partially degraded dithranol preparations.

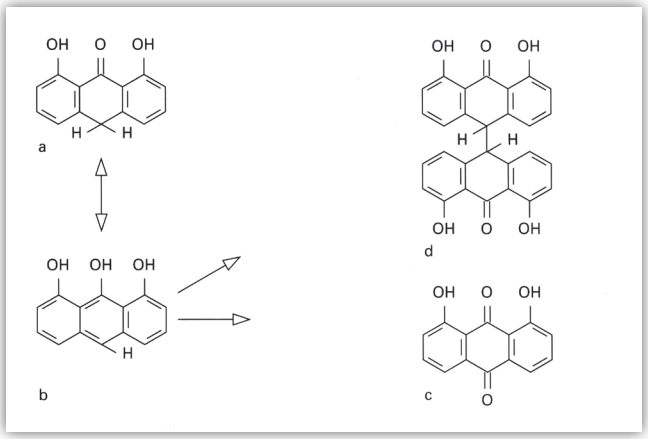

Figure 9.4. Degradation of dithranol (a, b) to 1.8-dihydroxyanthraquinone (c) and 1.8.1′.8′-tetrahydroxydianthron (d)

9.4.3 Reaction kinetics

In the literature no quantitative reaction parameters were found to calculate the shelf life of dithranol and its preparations. This applies to most drugs degrading by oxidation, because the reactions depend on too many variables to allow general calculations. Stability must therefore be evaluated in the final product, packed in the final container. Some qualitative remarks on dithranol are relevant to consider.

a. Degradation of dithranol increases at higher pH values. Dissociation seems to play a role; this is consistent with the fact that the more acidic hydroxy group at position 9 is attacked first. Polymerisation reactions are fast at high alkaline pH values. This explains the discolouration of clothing and bedding when alkaline soaps are used prior to contact with dithranol. For the same reason discoloration of the skin occurs when alkaline soap is used to wash away dithranol containing preparations from the skin (25).
b. Oxygen radicals initiate the degradation reaction. The exclusion of oxygen (airtight packaging or packaging under nitrogen) slows down degradation of dithranol, but cannot prevent it (22,23). The addition of antioxidants and complex forming agents to capture catalysing heavy metals has a stabilising effect.
c. Light increases degradation.
d. Dithranol which is bound to protein is rapidly degraded (23). Whether this plays a role in its therapeutic activity is unclear.
e. Zinc oxide increases the degradation of dithranol. This is prevented by adding 2% salicylic acid. Whether the degradation reaction is due to alkaline impurities or to trace amounts of radical initiators, such as peroxides or heavy metals, is unclear.

9.4.4 Stability of dithranol in preparations

In the absence of light, oxygen or catalysts (radical initiators like peroxides and heavy metals), dithranol is fairly stable (22). Therefore it must be stabilised in most preparations. Only when dithranol is used in petrolatum or ambiphilic creams, stabilisation is not required.
Zinc oxide containing preparations, such as dithranol paste, require stabilisation with 2% salicylic acid. Salicylic acid is also an appropriate stabiliser for dithranol in fatty ointments. Creams with dithranol are stabilised with ascorbic acid. This formulary includes a stabilised cream with a shelf life of 2 months when stored below 25 °C, and a stabilised ointment with a shelf life of 3 months at less stringent storage conditions, i.e., preferably below 40 °C. Both formulations are based on the *Dutch Formulary* (27).

9.5 Stability of hydrocortisone and other corticosteroids

9.5.1 Introduction

Corticosteroids are used for the treatment of many diseases. Specific corticosteroids were developed for skin diseases. Such steroids are more lipophilic by masking the hydrophilic hydroxyl groups at positions 17 and 21 (see figure 9.5). This improves penetration of the corticosteroid into the skin. Consequently, ester hydrolysis results in less effective corticosteroids.

Degradation reactions also occur in the steroid skeleton. Esters may prevent degradation reactions at the steroid skeleton, but this is not a general rule.

9.5.2 Corticosteroid degradation

Corticosteroid skeletons are degraded by a great number of reaction mechanisms. For a given steroid the mechanism depends on the reaction medium. Generally the side chain at position 17 is the most reactive part of the molecule, but degradation also occurs at the A-ring. In situations usually encountered in pharmaceutical practice, degradation at the 17 side chain determines the overall stability (28,29).

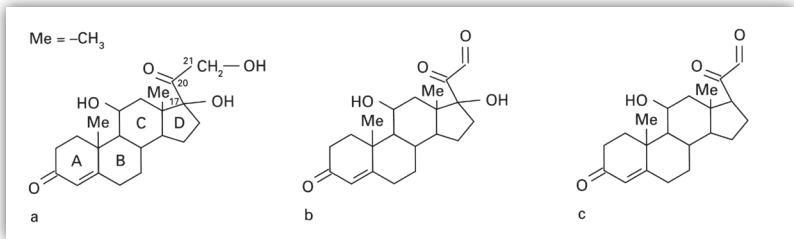

Figure 9.5. Molecular formula of hydrocortisone (a); degradation products of hydrocortisone: 21-dehydro-hydrocortisone (b) and 17-deoxy-21-dehydro-hydrocortisone (c)

The following comments on hydrocortisone are generally valid for most corticosteroids.

a. In an acidic medium degradation occurs through a non-oxidative, acid catalysed reaction, resulting in the formation of 17-deoxy, 21-dehydrohydrocortisone (a glyoxal, see figure 9.5). This reaction is not influenced by heavy metals or oxygen (30).
b. In a neutral to slightly acidic medium degradation occurs through two competing reactions, the acid catalysed non-oxidative reaction described above, and an oxidative reaction resulting in the formation of 21-dehydrohydrocortison (see figure 9.5) which is also a glyoxal. The latter reaction is influenced by heavy metal traces or oxygen. These glyoxals are unstable compounds which are further degraded (31).
c. In an alkaline medium a great number of competing degradation reactions occur, depending on the presence of catalysts, light and pH (29). These may or may not be oxidative. Glyoxals are formed in alkaline media as well.

The glyoxals resulting from corticosteroid degradation are reactive substances. They react with proteins (arginine) and the resulting denaturation of the protein may provoke an allergic reaction. This is thought to be the general mechanism involved in corticosteroid allergy (31). The incidence of such reactions is very low, but is likely underreported as corticosteroids mask allergic responses.

9.5.3 Degradation kinetics

Generally valid degradation kinetics of corticosteroids cannot be given as degradation depends on too many, often unknown factors, and many reaction mechanisms are involved. Apparent reaction parameters for overall degradation are a summation of all separate reactions. Some apparent reaction parameters at neutral pH were determined by Hansen and Bundgaard. Based on their findings, the estimates for the shelf life of hydrocortisone preparations are approx. 250 days at 20 °C, and 130 days at 25 °C. This increases to approx. 160 days at 25 °C when sodium edetate is added to capture heavy metals which increase reaction rates. At 40 °C, which is the appropriate kinetic average temperature in the tropics, the shelf life of aqueous solutions of hydrocortisone is only 3 weeks. Hydrocortisone is most stable at pH 4 (28).

9.5.4 Stability of hydrocortisone in some preparations

Hydrocortisone is unstable in the presence of polyethylene glycols. This is due to the presence of peroxides catalysing various degradation reactions, or to the presence of minute heavy metal contaminations (35). Therefore polyethylene glycol ointment bases are inappropriate for corticosteroid preparations.

Hydrocortisone is less stable in preparations containing zinc oxide (34). In shake lotions the high alkalinity accounts for fast degradation, but an effect of heavy metal impurities or zinc peroxides may also play a role. Finally, adsorption of steroid on zinc oxide particles occurs.

Corticosteroids (hydrocortisone, prednisolone) are less stable in preparations containing urea. This is due to the higher pH value of such preparations, but an additional specific effect of urea or its impurities cannot be ruled out (36).

The above mentioned instabilities are likely to be an issue for all corticosteroids. Although particular steroids are somewhat more stable than others, they all exert the same degradation pattern and basically their stability is comparable (35). Commercially available corticosteroid preparations are stabilised with specific compounds. Dilution of such products compromises their stability and likely results in decreased therapeutic activity. This practice should therefore be avoided.

9.5.5 Corticosteroid ester hydrolysis

Corticosteroid esters are generally used in dermatology. As the esters penetrate better into the skin compared to the corresponding steroids, they are usually more active. Hydrolysis of such esters therefore decreases the activity of the preparation. Specific toxicity of the hydrolysis products is not expected.

Apart from total hydrolysis which is usually slow, intramolecular rearrangements occur. This has for example extensively been documented for betamethasone-17-valerate in older literature (37-42). The molecular structure favours rearrangement of betamethasone-17-valerate to the more stable 21-valerate. Subsequently the 21-valerate slowly hydrolyses to the corresponding free corticosteroid. Rearrangement of betamethasone-17-valerate occurs both in the presence and absence of water, and is a fast process (35). The stability is relatively good in petrolatum and ambiphilic creams (42,43). Albert (44) also reported a good chemical stability of various unstable drugs in ambiphilic creams.

Betamethasone-17-valerate is about 20 times more active than the 21-valerate, and a dramatic decrease in therapeutic activity results from the rearrangement reaction. The reaction is expected for all 17-monoesters with a free hydroxy group at position 21, but not in 17-monoesters without such a free hydroxy group (clobetasol propionate), not in 17,21-diesters (betamethasone dipropionate), and not in 21-monoesters (hydrocortisone acetate).

9.5.6 Corticosteroid acetonides

The stability of corticosteroid acetonides (triamcinolone acetonide, fluocinolone acetonide) as reported in the literature, is comparable to that of the corticosteroid itself (35). Rearrangements are not likely to occur and acetonide instability is not expected to be an issue.

9.5.7 Conclusions

In tropical climates extemporaneous corticosteroid preparations have a limited shelf life of 1 month at the most. Preparations should therefore be made immediately before dispensing. Provided proper packaging, the raw materials are fairly stable and may be held in stock for about 2 years. The main risk resulting from degraded corticosteroids is decreased activity. Increased allergic potential may occur, but as glyoxals are unstable their concentrations are low and essentially constant in most corticosteroid preparations.
17-Monoesters such as betamethasone-17-valerate are relatively unstable and are better avoided. Commercial formulations are optimised for stability and may have better stability than extemporaneous preparations. The dilution of commercial formulations likely results in loss of their specific stabilising properties and should therefore be avoided.

9.6 Stability of phenolic compounds

9.6.1 Introduction

Various phenolic compounds (see figure 9.6) are widely used in dermatological preparations. Phenol, for example, is used in calamine lotion. It serves multiple purposes in this preparation, i.e., preservation and antipruritic activity. Phenol has a limited stability. The packaging material is important.

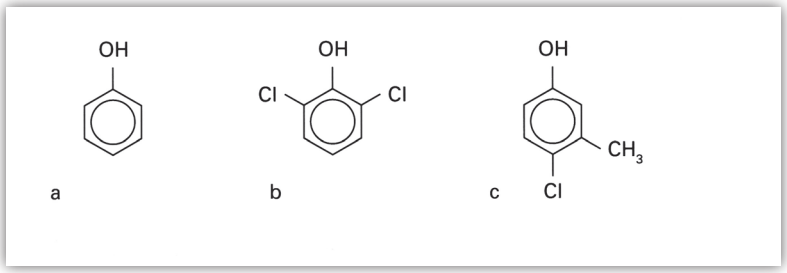

Figure 9.6. Molecular formulas of phenol (a), dichlorophenol (b) and chlorocresol (c)

9.6.2 Degradation of phenols

Phenols are degraded by oxidative reactions. The reaction rates increase by traces of heavy metal ions, light and oxygen. The stability of phenol in aqueous solution stored in bottles was found to be dependent on the packaging materials. After twelve weeks storage of an aqueous phenol solution in glass 100.9% phenol remained (due to some water evaporation the original phenol concentration increased a bit), in rigid PVC 99.8%, and in polyethylene (common plastic) 91.1%. Thus, plastic bottles are inappropriate for the packaging of aqueous solutions of phenolic compounds (47,48).

Pure phenol degrades rapidly upon exposure to air or light. Degraded phenol is coloured pink to red. Phenol with a slightly pink colour can still be used but deeply coloured phenol should be discarded. Kept in airtight containers in the dark, phenol can be stored for some years. An estimated maximum shelf life for phenol containing preparations is 6 months.

9.7 Stability of sorbic acid in solutions

9.7.1 Introduction

Sorbic acid (see figure 9.7) is widely used as a preservative in pharmaceutical preparations, especially in dermatologicals and food products. It is unstable.

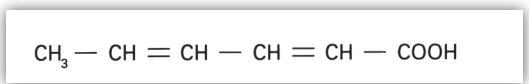

Figure 9.7. Molecular formula of sorbic acid

9.7.2 Physical stability

Sorbic acid is volatile at temperatures above 75 °C in the presence of water. The effect does not occur in solutions stored at ambient conditions. In the process of boiling water for the preparation of creams, evaporation of sorbic acid is likely to occur. Boiling water is necessary to reduce contamination, and to ensure complete dissolution of the sorbic acid. While preparing creams with sorbic acid, precautions are required to keep evaporation to a minimum. Sorbic acid should therefore be dissolved in freshly boiled water that is still hot, but not boiling anymore. Also, the container should be kept closed during the cooling process.

9.7.3 Degradation reactions

Degradation of sorbic acid occurs through several free radical, oxidative, reaction mechanisms. Not all mechanisms involved are fully clarified yet (49,51,52). Different degradation products are formed, some of which are expected to have antimicrobial activity (53). The pH is a determining factor in the degradation of sorbic acid. Degradation is less at higher pH values. This is caused by the electron distribution in dissociated sorbic acid which is less favourable for degradation (50). Due to inactivity of sorbic acid at higher pH, it is not a feasible stabilisation method.

Oxygen increases the degradation of sorbic acid. A relationship was found between the permeability of the packaging materials for oxygen and the stability of sorbic acid. Light also increases degradation (47,48). Antioxidants are used to stabilise sorbic acid solutions. Stabilisation of aqueous solutions has been reported, probably due to released antioxidants from packaging materials (47,48). Some emulsifiers, for instance polysorbate 80, increase the degradation of sorbic acid (54).

Water is necessary for the degradation of sorbic acid. In the absence of water it is reasonably stable (51). Highly concentrated solutions have a lower water activity, meaning that the water in such preparations is less able to react. In concentrated solutions, for example syrups, the degradation of sorbic acid slows down, but this is not a general rule as polyols also increase degradation (51).

The packaging material largely affects the stability of sorbic acid solutions. They protect sorbic acid directly by limiting the exposure to air and light. Antioxidants that are released from the packaging material exert a protective effect on the stability of the solution.

9.7.4 Degradation kinetics

Degradation of sorbic acid follows (pseudo) first order kinetics (50,51). As in other oxidative degradation processes, it is very difficult to calculate the degradation parameters accurately. Stability studies should therefore be done with the final product in its final packaging.

Arya determined the stability of sorbic acid in aqueous solutions. The shelf life at 37 °C calculated from his data is 50 days at pH 5 and 25 days at pH 4. Iron, copper, manganese and sodium chloride decrease degradation rates (50). Seow and Cheah determined the degradation at pH 4 in solutions with a high sugar content. Based on their measurements the shelf life at 40 °C is 7 days (51). These data clearly indicate that the stability of sorbic acid solutions is a potential issue in tropical conditions.

9.7.5 Conclusions

At the kinetic average temperature in tropical countries sorbic acid is unstable. This limits its usefulness in dermatological preparations for tropical conditions. Sorbic acid containing preparations have a shelf life of

1 month at best. Because sorbic acid is volatile in the presence of water, special precautions are necessary during the preparation of creams.

9.8 Stability of urea

9.8.1 Introduction

Urea is widely used in dermatology, but it is unstable. A good understanding of its degradation reactions is necessary to estimate the shelf life for urea containing preparations.

9.8.2 Degradation of urea

Urea degrades through two consecutive hydrolysis reactions (see figure 9.8). The first reaction (figure 9.8a) is reversible and an equilibrium is formed (56,57).

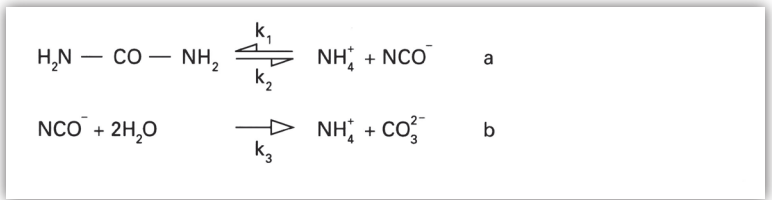

Figure 9.8. Degradation reactions of urea

The overall kinetic parameters of the degradation of urea have not been described. Authors use different definitions of urea degradation, such as the formation of cyanate, the degradation of urea, the formation of carbonic acid, the formation of cyanate and carbonic acid, etc. Two additional factors complicate the picture further. The first is the impossibility to carry out accelerated stability studies because the relationship between the temperature and overall reaction rate is very complicated. Too many processes are involved, such as the reactions a) and b) in figure 9.8, the evaporation of ammonia and carbon dioxide, and dissociation reactions. The second complicating factor is that degradation is dependent on the initial concentration of urea (57-59).

Urea solutions are stabilised with lactic acid, triacetin or polysaccharides. Polysaccharides are most appropriate (36). However, these stabilisers influence the therapeutic activity and/or safety. It is therefore better to use urea preparations without stabilisers and to limit the shelf life as a consequence.

9.8.3 Conclusions

Urea preparations should be freshly prepared and should not be stored for more than 1 month. Without water urea is relatively stable; when adequately packed in airtight packaging/containers to prohibit moisture absorption from the air, urea can be kept for more than 2 years.

9.9 Summary of stability data

The following tables summarise the stability data of all materials that are used in this formulary.

Table 9.2. Chemical stability data of all raw materials included in this formulary

Material	*Medium*	*Teff.*	*Shelf life*	*Deg. mech.*
Bentonite		*> 32.4 ºC*	*> 2 years*	
Benzoic acid		*> 32.4 ºC*	*> 2 years*	
Benzyl benzoate	*raw material*	*> 32.4 ºC*	*> 2 years*	
	emulsion	*> 32.4 ºC*	*2 years*	*h*
Chlorhexidine	*aq. solution*	*> 32.4 ºC*	*2 years*	*h*
	acetate dry	*> 32.4 ºC*	*> 2 years*	
Dithranol	*aq. solution*	*> 40.0 ºC*	*max. 7 days*	*o*
	stabilised aq. solution	*> 40.0 ºC*	*1 month*	*o*
	raw material dry	*> 33.6 ºC*	*1 year*	*o*
Gentian violet		*> 32.4 ºC*	*> 2 years*	
Glycerin		*> 32.4 ºC*	*> 2 years*	
Hydrocortisone acetate	*aq. solution*	*> 40.0 ºC*	*20 days (pH=5)*	*h, o*
	raw material dry	*> 33.6 ºC*	*1 year*	*h, o*
Iodine		*> 32.4 ºC*	*> 2 years*	
Lanette wax SX		*> 32.4 ºC*	*> 2 years*	
Lindane		*> 32.4 ºC*	*> 2 years*	
Miconazole		*> 32.4 ºC*	*> 2 years*	
Nystatin	*aq. solution*	*> 40.0 ºC*	*max. 7 days*	*o*
Oil (vegetable)		*> 33.6 ºC*	*1 year*	*o*
Parabens	*aq. solution*	*> 32.4 ºC*	*> 2 years (pH 3-6)*	
	raw material dry	*> 32.4 ºC*	*> 2 years*	
Paraffins		*> 32.4 ºC*	*> 2 years*	
Phenol	*raw material dry*	*> 32.4 ºC*	*2 years*	*o*
	aq. solution	*> 33.6 ºC*	*6 months*	*o*
Potassium permanganate	*aq. solution*	*> 40.0 ºC*	*max. 7 days*	*o*
	raw material dry	*> 32.4 ºC*	*> 2 years*	
Salicylic acid		*> 32.4 ºC*	*> 2 years*	
Silver nitrate	*aq. solution*	*> 40.0 ºC*	*max. 7 days*	*o*
	raw material dry	*> 32.4 ºC*	*> 2 years*	
Sodium citrate		*> 32.4 ºC*	*> 2 years*	
Sodium thiosulphate	*aq. solution*	*> 40.0 ºC*	*max. 7 days*	*o*
		> 32.4 ºC	*> 2 years*	
Sorbic acid	*aq. solution*	*> 40.0 ºC*	*1 month*	*o*
	raw material dry	*> 32.4 ºC*	*2 years*	*o*
Sulphur		*> 32.4 ºC*	*> 2 years*	
Tar		*> 32.4 ºC*	*> 2 years*	
Urea	*aq. solution*	*> 40.0 ºC*	*1 month*	*h*
	raw material dry	*> 32.4 ºC*	*> 2 years*	
Zinc oxide		*> 32.4 ºC*	*> 2 years*	

Abbreviations used are:
aq. = aqueous;
sol. = solution;
stab. = stabilised;
> = more than;
h = hydrolysis;
o = oxidation/reduction reactions;
teff. = kinetic average temperature;
deg. mech. = degradation mechanism

Shelf life is defined as the time in which 10% degradation occurs.
For unstable compounds, the degradation mechanism is indicated.

Table 9.3. Physical stability of raw materials. The asterisk * indicates the stability issues that are encountered upon decay

Material	***Hygroscopic***	***Volatile***	***Melting***	***Crystallisation***
Bentonite	*			
Benzoic acid		*		
Benzyl benzoate				*
Chlorhexidine				
Dithranol				
Gentian violet	*			
Glycerin	*			*
Hydrocortisone acetate				
Iodine		*		
Lanette wax SX			*	
Lindane		*		
Miconazole				
Nystatin	*			
Oil (vegetable)				
Parabens				
Paraffins				
Phenol	*	*		
Potassium permanganate				
Salicylic acid		*		
Silver nitrate				
Sodium citrate	*			
Sodium thiosulphate	*			
Sorbic acid		*		
Sulphur				
Tar		*		
Urea	*			
Water		*		
Zinc oxide	*			

9.10 General literature

General information in English on the principles of stability and shelf life can be found in *Aulton's Pharmaceutics* (1), the *Pharmaceutical Codex* (35) and *Martindale* (60). Detailed information in English is available in *Connors' Chemical Stability of Pharmaceuticals* (61). The information is also based on sources in the Dutch and German languages (62-64).

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10 Vocabulary

Difficult words and technical terms are not avoided in the book and the formulary. Technical terms that are used in the chapters with practical information, i.e., the chapters 3, 6, 7, 8, 12 and 13, are explained in this vocabulary.

abdominal pain belly pain
absorption process in which a substance penetrates into the body, either through the skin, or after ingestion.
acidic having the characteristics of an acid. An **acid** is a water soluble compound having a sour taste, in solution it turns litmus paper red, and it is able to react in solution with a base to form a salt
accurate correct, making no mistakes
adjacent next to, neighbouring
adverse reactions unwanted reactions, also referred to as side effects when involving medicine
aggregates collection of separate particles clustering together and forming one mass
aggressive said of a substance that attacks many materials, including human skin
albino a person with a genetic inability to form pigment, as a result skin and hair are white and eyes pink
alkaline basic, having the characteristics of a base. A **base** is a water soluble compound that is able to turn litmus blue and reacts with an acid to form a salt
analgesic pain killer, medication against pain
anhydrous free from water
anti-coagulant slows down blood clotting
anti-inflammatory medication to reduce inflammation. **Inflammation** is the response of the body, or body part, to irritation or injury, characterized by swelling, redness, pain and heat
antimycotic medication against a fungal infection
antipruritic medication against itch
antiseptic a substance used to kill micro-organisms on the human skin
appropriate suitable
astringent property of a substance that tends to draw together or constricts tissue
athlete's foot is a fungal infection of the feet, causing scaling, flaking and itch. It is usually acquired by walking on moist surfaces such as showers. It may spread to other parts of the body
autoclave to sterilise by boiling under pressure, apparatus used to sterilise by boiling under pressure
balance an instrument for weighing
base a compound that is able to turn litmus blue and reacts with an acid to form a salt
batch a group of things made at the same time
batch number a specific number given to each product of the same batch
blood coagulation blood clotting
bullous eruption eruption characterized by bullae. **Bullae** are large vesicles. **Vesicles** are elevations of the epidermis containing fluid, such as blisters
calibrate to correct an instrument so that it may be used for precise measurements
callus where the skin has become thick and hard, generally due to pressure
candidosis infection with a yeast of the *Candida* sp. family
carcinogenic a substance that can cause cancer
cardiovascular system total system of heart and blood vessels
caustic corrosive, said of a substance that attacks, eats away, certain materials

coma a state of deep unconsciousness, usually after intoxication, injury or disease
consistency thickness, texture
contact dermatitis a hypersensitive skin reaction that develops after contact with a substance
container a container is anything, such as a box, bag, tin or pot, into which things can be kept
contamination dirtiness or infection caused by contact
convulsion uncontrollable, usually strong, contraction of muscles
corn where the skin has become thick and hard, generally due to pressure
corrosive said of a substance that attacks, eats away, certain materials
CNS central nervous system, consists of brain and spiral cord
cream a soft, wet mixture of fats and water
degradation break down, decomposition
deliquescent able to become liquid after dissolving in moisture absorbed from the air
density weight per volume, heaviness
depigmentation loss of pigment from the skin, formation of white, or lighter, patches on the skin
depression pushing down, lowering. Also a mental state characterized by lack of initiative, pessimistic views and low self esteem
dermatitis inflammation of the skin. **Inflammation** is the response of the body, or body part, to irritation or injury, characterized by swelling, redness, pain and heat
disinfectant a substance used to kill micro-organisms
dispense to sell or hand out medicines
dissolve to cause some solid matter to disappear in a liquid
dose the amount of medicine that should be taken by or given to a patient
eczema general term for inflammation reaction of the skin. **Inflammation** is the response of the body, or body part, to irritation or injury, characterized by swelling, redness, pain and heat
efflorescent flowering, bursting
emollient a preparation that hydrates the skin and makes it softer
emulsifying producing an emulsion. An **emulsion** is a homogeneous mixture of fats, water and emulsifying agent
emulsion a homogeneous mixture of fats, water and emulsifying agent
epidermis the outer layer of the skin
equivalent the same as, comparable to
eruption sudden, often spontaneous, occurrence or appearance
evaporation liquid changing into gas
exacerbation worsening of an existing condition
excessive unlimited, beyond usual limits, unrestrained
excitation state of agitation and arousal
expiry date date whereupon the quality of a product can no longer be guaranteed
extemporaneous extemporaneous preparations are dispensed immediately after production
extensive use use on a large scale, of large amounts, on a large part of the body
external use use on the skin
fissure long, narrow crack
folliculitis inflammation of a hair follicle. The hair follicle is the base where a hair is growing from
forceps tweezers, small instrument to pick up small things
formula a list of ingredients and the amounts to be taken
fungistatic a substance that is able to slow down the growth of a fungus. A **fungus** is a micro-organism usually feeding on organic material that may cause diseases when feeding on (skin) tissue

gastric lavage washing out the stomach with water or another suitable liquid using a gastric tube
gradually part by part, not at once
Gram positive organism bacteria that are coloured using the Gram colouring technique
growth retardation when a child does not grow as much as it normally should
hazard danger
homogeneous completely mixed
hydrate to wet the skin through and through
hyperkeratotic too much keratinisation. Keratinisation is the process of building up the horny layer of skin by depositing keratin in the cells
hypochloremia when there are not enough chlorine ions in the blood
hypopigmentation loss of pigment from the skin, formation of white, or lighter, patches on the skin
hygiene general cleanliness
ichthyosis a skin condition with a scaly, flaky, dry, thickened skin, generally on large parts of the body, often genetic
impotence inability to have sexual intercourse
immunologic referring to the immune system. The **immune system** protects the body against micro-organisms
indifferent containing no active ingredient
inferior of a lesser quality
infection an invasion of disease causing micro-organisms into the body or part of it
infestation massive invasion of the body with parasites
inflammation is the response of the body, or body part, to irritation or injury, characterised by swelling, redness, pain and heat
ingestion swallowing, eating
inhalation breathing in
inhomogeneous not completely mixed, partially separated
insomnia inability to sleep
intermittent alternately using two or more different preparations
intoxication poisoning
intravenous injection directly into a vein
irritation pain or burning sensation due to contact with a substance. Irritation is due to slight cellular damage. Irritation may develop in everybody (compare sensitisation)
isotonic having the same tonicity or osmotic pressure as body fluids and tissues, which is necessary when a fluid directly contacts body cells, for example after injection
keratolytic dissolving the outer, horny, layer of the skin
keratoplastic softening the outer, horny, layer of the skin
lactation breast feeding
leprosy infection with *Mycobacterium leprae*, characterised by inflamed nodules under the skin. Leprosy progressively leads to damage of skin, nerves, limbs and eyes
level a certain height, resembling a certain amount
lotion a liquid preparation, it may be a solution, emulsion or suspension
manufacturing process a series of actions by which a product is made
measure an instrument for volume measurements
measurement the determination of length, weight, volume etc. of something
metabolic acidosis abnormally high acidity of blood and tissue resulting from abnormal accumulation of acids or loss of bases from the body

methaemoglobinaemia abnormally high concentration of methaemoglobin in the body. Methaemoglobin is an oxidised form of haemoglobin with less capacity to transport oxygen in the body
microbial count number of micro-organisms present
micro-organisms tiny germs that can only be seen with a microscope and that can cause infections. Bacteria, fungi and yeasts are micro-organisms
mixing to put different things together so that they form one substance
mixing efficiency resulting in a good quality of mixing
moisturiser a preparation that hydrates the skin
monograph a piece of text about one particular preparation or material
mucosa mucus secreting membrane that lines all body cavities open to the outside
muscle spasm uncontrollable, usually strong, contraction of muscles
mutagenic a substance that causes damage to the genes. Such substances may also be carcinogenic and teratogenic
mycotic fungal, referring to a fungus
nausea sick feeling preceding vomiting or throwing up
necrotic dead cells or tissue
non-ionic surfactant type of emulsifier that does not form ions in aqueous surrounding
occlusive closing the skin off from the outside
ointment a soft mixture consisting mainly of fats
oral through the mouth
organic matter having properties of, or being derived from, living organisms. Examples are cotton wool and paper
parakeratotic changing the outer layer of the skin
parasite an organism that lives off another living organism, usually said of small insects that feed on humans or cattle
paste a soft mixture of a powder and a liquid or a semisolid that is easily spread
peritonitis inflammation of the peritoneum. The **peritoneum** is the tissue lining the abdominal wall
pH value value for the acidity of a solution
pharmaceutical concerning medication
pharmacopoeia a book containing specifications and regulations concerning medicines
photodermatosis skin disease caused by exposure to sunlight
photosensitisation sensitisation due to the combination of a drug and sunlight. When exposure to sunlight is avoided, sensitisation will not occur
phototoxicity toxic reaction due to the combination of a drug and sunlight. When exposure to sunlight is avoided, toxic reactions will not occur
pictogram a drawing or painting that is used to give information
pigment substance producing colour, for example melanin which causes human skin colouration and protects us from photodermatosis
pipette an instrument for measurement of small volumes
pityriasis versicolor a skin disease caused by a fungus
placenta the vascular structure that ensures the exchange of oxygen, nutrients and waste between a pregnant woman and her unborn child, afterbirth
premises buildings
preservative a substance able to prevent the growth of micro-organisms. It is added to a number of preparations to prevent microbial spoilage
properties qualities or attributes of a material

proprietary branded, protected by patents or trade marks
pruritus itch
psoriasis a chronic, non-infectious skin disease characterized by dry, red patches covered with scales
purgative medication that strongly promotes evacuation of the bowels, strong laxative
pyoderma a skin condition characterised by pus production, usually caused by infection
quality how well something has been done
quantity the amount of material
raw material starting material, the substance(s) from which a product is made
resistance when microbes or parasites are no longer killed by a medicine, they are said to be resistant
respiration breathing
respiratory alkalosis excess of base or lack of acid in the body caused by breathing problems
respiratory failure when the lungs stop functioning properly
ringworm a skin condition caused by an infection with a fungus
seizure a sudden attack
S.I. unit system a set of units used internationally. It comprises for example the metre and the kilogram
semisolid a soft material, halfway between a solid and a liquid. It cannot be poured like a liquid but it isn't hard like a solid either
sensitisation reaction of the body to repeated contact with a substance, with pain, redness or itch. Sensitization is not due to damage. It develops in a few persons only (compare irritation). After repeated contact with a substance to which a person has been sensitised, an allergic reaction is elicited
separation two things going away from each other. Also the inverse of mixing
shelf life the period in which a certain preparation can be kept in store
side effects unwanted effects resulting from the use of a medicine
sieve an object with a wire network stretched across the bottom of a frame. It is used to separate small objects, which fall through, from large objects, which stay on the frame
solubility to what extend a specific solid can be dissolved in a specific liquid
solution a liquid in which a solid is dissolved
spoil to waste
sterilisation to make free from living micro-organisms, usually by boiling or heating
stock a quantity of goods kept in store
suction bulb a rubber bulb used to draw liquid into a pipette
superficial only concerning the outer part of the skin
supportive treatment treatment to keep a critically ill patient alive for example by assisted breathing
surfactant emulsifier
suspension a mixture of a liquid and a solid that does not dissolve in it
symptomatic only aimed at taking away the symptoms of the disease and not at curing the underlying disease. **Symptoms** are the outer signs of a disease
synonyms different words with the same meaning
systemic of internal parts of the body
tare (said of a balance) set to zero or brought into balance
teratogenic harmful for the unborn child (foetus)
tincture a solution that contains alcohol
topical treatment treatment with preparations applied to the place where the problem is, often the skin
toxic poisonous, a substance which causes sickness
triturate to rub between the wall of a mortar and a pestle
ulceration an inflammatory lesion of the skin or mucosa resulting in necrotic tissue

ultraviolet rays invisible radiation, part of the radiation spectrum of the sun
unit an amount or quantity taken as a standard of measurement. In production unit: production facility, production centre
vascular collapse total breakdown, fall over, due to failure of the cardiovascular system
vehicle preparation before the active ingredient is added, the means to get the active ingredient applied to and absorbed by the skin
vessel a container, usually for liquids
virus very small infectious organism that can only duplicate inside the cells of another organism
viscous having a relatively high resistance to flowing
vitiligo a skin condition characterized by depigmentation of skin patches
volume the measure of space taken up by something
volumetric glassware glassware used for measuring volume
waxed paper paper with a layer of wax on it, used to weigh fatty substances
weigh to find the weight of a certain amount
weight the heaviness of something, also an object with a standard heaviness

11 Synonyms

This chapter lists the synonyms of the dermatological preparations (chapter 12) and raw materials (chapter 13) included in the book and formulary. The term generally used is indicated in **bold**.

acido ortoxibenzoico – **salicylic acid**
acidum citricum monohydricum – **citric acid monohydrate**
alcohol – **industrial methylated spirit**
aluminium magnesium silicate – magnesium aluminium silicate, saponite
anthralin – **dithranol**
argenti nitras – **silver nitrate**
ascorbic acid – vitamin C

bentonite – mineral soap, soap clay, wilkinite
benzoic and salicylic acid cream – **whitfield's cream**
benzoic and salicylic acid ointment – **whitfield's ointment**
benzyl benzoate application – **benzyl benzoate emulsion**
benzyl benzoate lotion – **benzyl benzoate emulsion**
blanc de zinc – **zinc oxide**

carbamide – **urea**
carbolic acid – **phenol**
cera emulsificans – **lanette wax**
CI basic violet 3 – **gentian violet**
CI pigment white 6 – **titanium dioxide**
citric acid monohydrate – hydrous citric acid, acidum citricum monohydricum, E330
coal tar – pix carbonis, pix lithantracis
colour index no 42555 – **gentian violet**
colour index no. 77891 – **titanium dioxide**
crystalviolet – **gentian violet**

1,8 dihydroxy 9 anthron – **dithranol**
dioxyanthranol – **dithranol**
dithranol – 1,8 dihydroxy 9 anthron, anthralin, dioxyanthranol

E171 – **titanium dioxide**
E218 – **methylparaben**
E330 – **citric acid monohydrate**
emulsifying wax – **lanette wax**
ethylhexyl methoxycinnamate – **octinoxate**
2-ethylhexyl (2e)-3-(4-methoxyphenyl)prop-2-enoate – **octinoxate**

flores de zinc – **zinc oxide**
flour of sulphur – **sublimed sulphur**

gamma BHC – **lindane**
gamma HCH – **lindane**
gamma hexachlorocyclohexane – **lindane**
gammabenzene hexachloride – **lindane**
gammexane – **lindane**
gentian violet – cl basic violet 3, colour index no 42555, crystal violet, hexamethylpararosaniline chloride, methylrosaniline chloride, pyoctaninum caeruleum
glycerin – glycerol
glycerol – **glycerin**

hexachlorocyclohexane cream – **lindane cream**
hexamethylpararosaniline chloride – **gentian violet**
hydrocortisone acetate cream – **hydrocortisone cream**
hydrocortisone acetate ointment – **hydrocortisone ointment**
hydrocortisone cream – hydrocortisone acetate cream
hydrocortisone ointment – hydrocortisone acetate ointment
hydrous citric acid – **citric acid monohydrate**
hydroxybenzene – **phenol**
2-hydroxybenzoic acid – **salicylic acid**

industrial methylated spirit – alcohol

kalium hypermanganicum – **potassium permanganate**
kalium iodidum – **potassium iodide**

lac sulphuris – **precipitated sulphur**
lanette wax – cera emulsificans, emulsifying wax
lindane – gamma benzene hexachloride, gamma BHC, gamma HCH, gamma hexachlorocyclohexane, gammexane

liquid paraffin – liquid petrolatum, oleum vaselini, vaselinum liquidum, white mineral oil
liquid petrolatum – **liquid paraffin**
liquefied phenol – phenol aqueux, phenol liquefactum

methyl hydroxybenzoate – **methylparaben**
methyl para-hydroxybenzoate – **methylparaben**
methylis oxybenzoas – **methylparaben**
methylparaben – methyl hydroxybenzoate, methylis oxybenzoas, methyl para-hydroxybenzoate, MOB, E218
methylrosaniline chloride – **gentian violet**
milk of sulphur – **precipitated sulphur**
mineral soap – **bentonite**
MOB – **methylparaben**
monobasic sodium phosphate – **sodium dihydrogen phosphate**

natricum nitrosum – **sodium nitrite**
natrii citras – **trisodium citrate**

nitrato de plata – **silver nitrate**

octyl methoxycinnamate – **octinoxate**
octinoxate – parsol MCX, OMC, octyl methoxycinnamate, ethylhexyl methoxycinnamate, 2-ethylhexyl (2e)-3-4-methoxyphenyl)prop-2-enoate
oleum vaselini – **liquid paraffin**
OMC – **octinoxate**

paraffinum molle – **petrolatum**
parsol MCX – **octinoxate**
petroleum jelly – **petrolatum**
petrolatum – paraffinum molle, petroleum jelly, soft paraffin, vaseline
phenol – carbolic acid, hydroxybenzene
phenol aqueux – **liquefied phenol**
phenol liquefactum – **liquefied phenol**
pinetar – **wood tar**
pix – tar
pix carbonis – **coal tar**
pix liquida – **wood tar**
pix lithantracis – **coal tar**
pix pini – **wood tar**
polyoxyethylene 20 sorbitan monooleate – **polysorbate 80**
polysorbate 80 – polyoxyethylene 20 sorbitan monooleate, sorbimacrogol oleate 300
polyvinylpyrrolidone-iodine – **povidone iodine**
potassium iodide – kalium iodidum
potassium permanganate – kalium hypermanganicum
povidone iodine – polyvinylpyrrolidone-iodine, PVP-iodine
precipitated sulphur – lac sulphuris, milk of sulphur
PVP-iodine – **povidone iodine**
pyoctaninum caeruleum – **gentian violet**

salicylic acid – acido ortoxicobenzoico, 2-hydroxybenzoic acid
saponite – **aluminium magnesium silicate**
silver nitrate – argenti nitras, nitrato de plata
soap clay – **bentonite**
sodium acid phosphate – **sodium dihydrogen phosphate**
sodium biphosphate – **sodium dihydrogen phosphate**
sodium citrate – **trisodium citrate**
sodium dihydrogen orthophosphate – **sodium dihydrogen phosphate**
sodium dihydrogen phosphate – monobasic sodium phosphate, sodium acid phosphate, sodium biphosphate, sodium dihydrogen orthophosphate
sodium hyposulphite – **sodium thiosulphate**
sodium nitrite – natricum nitrosum
sodium thiosulphate – sodium hyposulphite
soft paraffin – **petrolatum**
sorbimacrogol oleate 300 – **polysorbate 80**

stockholm tar – **wood tar**
sublimed sulphur – flour of sulphur
sulphur lotion – sulphur/calamine lotion

tar – pix
titanium dioxide – ci pigment white 6, colour index no. 77891, E171
trisodium citrate – natrii citras, sodium citrate

urea – carbamide

vaseline – **petrolatum**
vaselinum liquidum – **liquid paraffin**
vitamin C – **ascorbic acid**

white mineral oil – **liquid paraffin**
whitfield's cream – benzoic and salicylic acid cream
whitfield's ointment – benzoic and salicylic acid ointment
wilkinite – **bentonite**
wood tar – pine tar, pix liquida, pix pini, stockholm tar

zinc oil – zinc oxide liniment
zinc oxide – blanc de zinc, flores de zinc, zinc white
zinc oxide liniment – **zinc oil**
zinc oxide paste – **zinc paste**
zinc paste – zinc oxide paste

12 Preparation monographs

All monographs of the dermatological preparations are listed in this chapter. The monographs have a general format including all information relevant for the production and dispensing of the preparations. The following headings are included:

Preparation name

synonyms

Contains: composition of the preparation.

Formulation

– All raw materials and the quantities required.

Preparation:

– Preparation methods are listed.
– More information is found in chapter 7, the general notes on production, chapter 8, basic pharmaceutical methods, and chapter 5, backgrounds on dermatological vehicles.
– For all dermatological preparations that are suitable for local production, a master production form was developed based on the preparation methods as described in this chapter. The production forms are found on the CD that is complementary to this book.
– Some preparation methods include optional sieving of powders. As the master production forms are set up to serve production units with limited facilities, the optional preparation steps are not included on the forms.

Packaging:

– General packaging instructions.
– Special packaging instruction for dispensing to the patient.
– If possible, the dispensing quantity per patient, see also chapter 3.

Storage:

– Optimal storage conditions; the term "should" indicates necessary requirements for storage, whereas "should preferably" indicates storage conditions which are strongly recommended.
– Maximum storage period (total storage, including the period of use by the patient).
– Possible changes that may occur during storage and their consequences.
– Signs of degradation, if any.
– Risks of using an expired preparation.

Therapy:

- For external use only.
- General information on therapeutic properties, indications (see chapter 3), related drugs etc. More information is found in chapters 4, 5 and 9.

Dose:

- Recommended dose and, if relevant, duration of the therapy.

Instructions for use:

- For external use only.
- All relevant information the health worker should tell the patient to enable correct use.
- 'Use before' date, or maximum period of safe use when relevant.

Precautions:

- All relevant precautions for patients to ensure safe use of the preparation.
- Precautions for handling hazardous raw materials during preparation are listed in chapter 13.

Pregnancy/breast feeding:

- Available information on the possible risks for the unborn or newborn child, when the preparation is used by the mother.

Side effects:

- Information on local and systemic side effects, and irritation or sensitisation potential of the preparation.

Intoxication:

- Any information on signs that may indicate systemic intoxication resulting from absorption through the skin following external use.
- Information on the treatment of intoxication after accidental ingestion (only included for liquid preparations).
- Any other relevant information.

Additional information:

This part contains miscellaneous additional information, such as:

- Information on the origin of the formula.
- Information on the reason for using specific raw materials.
- Information on alternative ingredients when certain raw materials are unavailable.
- When relevant: information on resistance.
- When relevant: information on non-drug treatment.
- Information on precautions when large amounts are prepared for stock.
- Information on other strengths used.

Basic cream

Contains: 15% lanette wax, 35% paraffins, 0.15% methylparaben and water.

Formulation

lanette wax SX		15	g
liquid paraffin		12.5	g
petrolatum		22.5	g
methylparaben		0.15	g
water	to	100	g

Preparation:

1. Melt together lanette wax, liquid paraffin and petrolatum over gentle heat and mix.
2. Heat this mixture to approximately 70 °C.
3. Boil sufficient water for 1 minute. Dissolve the methylparaben in 50 ml of this boiling water. Allow the rest of the boiled water to cool.
4. Allow the methylparaben solution to cool to approximately 70 °C.
5. Add this solution to the fat mixture (2.) at a temperature of approximately 70 °C and mix.
6. Stir gently until cold.
7. Add enough recently boiled and cooled water to produce 100 g cream. Mix until homogeneous.

Packaging:

– Basic cream should be packed in a well closed container, which prevents the evaporation of water and the contamination with micro-organisms. The packaging should allow stirring of the cream. Basic cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.
– When inhomogeneous, basic cream should be mixed until homogeneous before dispensing from stock.

Storage:

– The cream should preferably be stored below 40 °C.
– The cream should preferably be used within 3 months.
– Expired creams may be contaminated with micro-organisms causing infections.
– Basic cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
– If the container is not closed properly, water may evaporate during storage. This results in an emulsifying ointment with a certain amount of water remaining. When the cream contains active ingredients, they will become more concentrated. The concentration will not rise above twice the original level. The changed properties should be taken into account when such creams are being used.

Therapy:

– For external use only.
– Basic cream is used as a vehicle for a number of active ingredients. It has a relatively high fat content. The cream is easily washed off with water, and is therefore suitable for hairy parts of the skin.

– Basic cream is not very occlusive, it may even have a slight drying effect on the skin. Basic cream is appropriate as indifferent preparation for intermittent treatment with strong corticosteroid preparations.

Dose:
– Apply in a thin layer several times daily.

Instructions for use:
– The cream should be applied in a thin layer. Excessively thick layers may cause some occlusion. Occlusion is generally unwanted as it may cause secondary infections and exacerbations of various skin diseases.
– If the cream is inhomogeneous, it should be mixed before use.
– Do not use past the expiry date, use within 30 days after dispensing.

Pregnancy/breast feeding:
– Harmful effects from external use of basic cream have not been reported.

Side effects:
– Side effects are rare. Sensitisation due to methylparaben may occur, but is rare with the concentration used in this cream. Sensitisation due to yellow petrolatum may occur, but is rare.
– Irritation due to lanette wax has been described. Inferior qualities of white petrolatum can also cause irritation. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

– The formula for basic cream is modified from the recipe in the *British Pharmacopoeia* for aqueous cream. Aqueous cream of the *British Pharmacopoeia* contains 30 g emulsifying ointment, 1 g phenoxyethanol and 69 g water. The basic cream we recommend is more stable at high temperatures than the original formula from the *British Pharmacopoeia*.
– 35% liquid paraffin or 35% petrolatum can be used instead of a mixture of the two. The mixture of the formula for basic cream results in the most stable product, and is therefore preferred.
– Methylparaben can be substituted by various other preservatives, for example 10% propylene glycol or 1% phenoxyethanol. However, methylparaben is preferred because of its favourable cost/effectiveness and risk/effectiveness balances.
– An easier way to prepare basic cream is using emulsifying ointment instead of lanette wax, liquid paraffin and petrolatum. The formula than reads: emulsifying ointment 50 g, methylparaben 0.15 g, water to 100 g. The preparation method remains essentially the same. From a pharmaceutical point of view, it is better to use the method described above in this monograph.

Benzyl benzoate emulsion 25%

benzyl benzoate lotion, benzyl benzoate application.

Contains: 25% benzyl benzoate in a water miscible emulsion.

Formulation

benzyl benzoate		25	g
lanette wax		2	g
water	to	100	ml

Preparation:

1. Boil 100 ml water for 1 minute and allow to cool to approximately 70 °C. Use this water for the preparation.
2. Melt together the benzyl benzoate and the lanette wax over gentle heat and warm to approximately 70 °C.
3. Add 70 ml of the water of 70 °C to this mixture and mix.
4. Stir gently until cold.
5. Add enough recently boiled and cooled water to produce 100 ml emulsion and mix well.

Packaging:

- Benzyl benzoate emulsion should be packed in well closed bottles, which prevent evaporation of water and contamination with micro-organisms, and protect the emulsion from exposure to light.
- Benzyl benzoate emulsion should be mixed until homogeneous before dispensing from stock.
- One adult patient needs 200 ml.

Storage:

- Benzyl benzoate emulsion should preferably be stored below 40 °C in a dark place.
- The emulsion may separate during storage. It should therefore always be shaken before dispensing or use. If carefully shaken this does not affect the quality of the emulsion.
- Benzyl benzoate emulsion should preferably be used within 3 months.
- Expired emulsions may be less effective.
- If the container is not closed properly, water may evaporate during storage. This results in an emulsion with a higher benzyl benzoate content, increasing the risk of side effects.

Therapy:

- For external use only.
- Benzyl benzoate emulsion is used for the treatment of scabies and lice.
- For the treatment of scabies lindane cream is preferred over benzyl benzoate emulsion because it only requires a single application to be effective. Due to environmental concerns lindane is no longer available in many countries. Some authors prefer benzyl benzoate emulsion for pregnant women (because lindane is thought to be teratogenic) and for children under the age of 3. For such treatments, sulphur 10% is also an alternative.
- For lice, non-drug treatment may be effective.

Dose:
- Scabies: apply the emulsion from the neck down to the whole body and repeat the application after 12 hours. Discard any lotion left.
- Lice: apply the emulsion three times, at weekly intervals. Discard any lotion left.

Instructions for use:
- Shake the bottle before use.
- Scabies: in the evening, take a hot bath and scrub the skin to open up burrows. Apply the lotion from the neck down to the whole body and rub it into the skin. Make sure the lotion gets into contact with the whole body, including skin folds. Wash hands after application. 12 hours later (the following morning) apply the emulsion a second time. 12 hours after the second and last application wash the body thoroughly with water and soap. Wash all clothes, bed sheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water, to prevent reinfestation. It is also recommended to shake out blankets and outer wear.
- Itch may persist for weeks after all the mites have been killed. Do not repeat treatment but use calamine lotion to relieve the itch.
- Lice: rub the lotion into all infected hairy areas and allow to remain for 24 hours. Wash off thoroughly, and comb the hair with a fine comb to remove dead lice. Wash all bed sheets, pillowcases and clothes, preferably in hot or boiling water and shake out blankets and outer wear. Repeat treatment twice at weekly intervals.
- Discard any remaining lotion.

Precautions:
- Scabies and lice usually affect more members of a household or community. As treating one of them is not effective, and a waste of time and money, try to treat all household or community members. As to pubic lice, treat all sexual partners.
- Avoid contact of benzyl benzoate emulsion with the eyes.

Pregnancy/breast feeding:
- Harmful effects from external use of benzyl benzoate have not been reported. However, evaluate the benefit/risk ratio before using this preparation during pregnancy or breast feeding.

Side effects:
- After frequent use of benzyl benzoate contact dermatitis may develop. This is not likely to occur after three applications. Sensitisation reactions are rare, irritation reactions with a burning or stinging sensation may occur. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Intoxication:
- After accidental ingestion benzyl benzoate causes central nervous system stimulation which may result in convulsions. Request for medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha. Convulsions are treated with diazepam.

Additional information:

- This formula was adapted from the formula used in the *British Pharmacopoeia* and the *Formulary of Dutch Pharmacists*.
- Lanette wax may be substituted by cetomacrogol wax.
- A preservative is not needed.
- Non-drug lice treatment consists of:
  - regular hair combing with a fine comb to remove lice.
  - regular washing of clothes, bed sheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water. It is also recommended to shake out blankets and outer wear.

Calamine lotion (modified)

Contains: zinc oxide 20% and phenol 0.4% in an aqueous vehicle.

Formulation

zinc oxide		20	g
bentonite		3	g
trisodium citrate		0.5	g
glycerin		5	ml
liquefied phenol		0.5	ml
water	to	100	ml

Preparation:

1. Boil 100 ml water for 1 minute and allow to cool. Use this water for the preparation of the lotion.
2. Dissolve the trisodium citrate in 70 ml of the water.
3. When sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
4. Mix the zinc oxide with the bentonite.
5. Triturate this zinc oxide/bentonite mixture with the glycerin and 20 ml of the citrate solution.
6. Add the rest of the citrate solution and mix until homogeneous.
7. Add the liquefied phenol and mix.
8. Add enough recently boiled and cooled water to produce 100 ml and mix well.

Packaging:

- Calamine lotion should be packed in well closed containers, which prevent evaporation of water and contamination with micro-organisms. Calamine lotion should be protected from exposure to light.
- Calamine lotion should be mixed until homogeneous before dispensing from stock.

Storage:
- Calamine lotion should preferably be stored below 40 °C.
- Calamine lotion should preferably be used within 3 months.
- Expired calamine lotions may be less effective, and may be contaminated with micro-organisms causing infections.
- Calamine lotion may separate during storage. It should always be shaken before dispensing or use.

Therapy:
- For external use only.
- Calamine lotion has general soothing, cooling, antiseptic and antipruritic properties. It is used for the treatment of itch, stinging or burning pain from insect bites, allergic reactions, or mild sunburn, and for various other skin diseases.

Dose:
- Apply the lotion several times a day, in acute disease up to a maximum of ten times a day.

Instructions for use:
- Shake the lotion before use. Calamine lotion should be painted onto the skin, for example with a brush. The lotion should then be allowed to dry. It should not be covered with wrappings or bandages.
- Do not use past the expiry date. Use within 1 month after dispensing.

Precautions:
- Calamine lotion should only be used on wounds with caution because of the risk of absorption of phenol.
- Calamine lotion should not be used on large parts of the body or for periods longer than 1 week unless prescribed by a doctor. Systemic side effects may result from absorption of phenol.
- Avoid contact of calamine lotion with the eyes.

Pregnancy/breast feeding:
- Harmful effects from external use of calamine lotion have not been reported. However, evaluate benefit/risk before using this preparation during pregnancy or breast feeding.

Side effects:
- Sensitisation reactions with a burning feeling are rare but may occur. When it occurs, stop using the lotion immediately.

Intoxication:
- When calamine lotion is ingested accidentally, request for medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

Additional information:

- The modified calamine lotion in this formulary originates from various pharmacopoeias, including the *British Pharmacopoeia*. The original formula of the *British Pharmacopoeia* contains 15% calamine and 5% zinc oxide, instead of 20% zinc oxide. Both formulations are equivalent, but the modified formulation is much cheaper.
- Instead of bentonite, aluminium magnesium silicate (Veegum®) may be used. The latter is a standardised branded product which is more expensive than bentonite.
- Other sodium citrates may be used instead of trisodium citrate. This will result in a preparation in which more zinc is dissolved. Such a preparation is more astringent and has a higher risk of side effects.
- Pure phenol can be used instead of liquefied phenol. To obtain the same concentration, use 0.4 g phenol instead of 0.5 ml liquefied phenol. Other preservatives are less suitable. Calamine lotion without a preservative should not be stored, but can be freshly prepared for immediate use. In addition to its preservative effects, phenol also exerts medicinal activity; calamine lotion without phenol is less effective.

Chlorhexidine diacetate solution 1%

Contains: 1% chlorhexidine diacetate in water.

Formulation

chlorhexidine diacetate		1	g
water	to	100	ml

Preparation:

1. Boil 120 ml water for 1 minute and allow to cool to 30 - 40 °C. Use this water for the preparation.
2. Dissolve the chlorhexidine diacetate in approximately 80 ml of the water and mix.
3. Check if all the chlorhexidine has dissolved.
4. Allow to cool completely.
5. Add enough recently boiled and cooled water to produce 100 ml and mix well.

Packaging:

- Chlorhexidine diacetate solution should be packed in a well closed container. Cork closures should not be used.
- The solution should be freshly prepared, unless sterilised.

Storage:

- Chlorhexidine diacetate solution should preferably be stored in a cool and dark place.

- Chlorhexidine diacetate solution 1% should preferably be used within 2 days. Sterilised solutions should preferably be used within 2 days after first opening. Unopened sterilised solutions and solutions containing at least 7% alcohol may be kept in store. These solutions should preferably be used within 3 months.
- Expired chlorhexidine solutions are less effective and may be contaminated with resistant micro-organisms. Contamination with micro-organisms is especially likely to occur after the packaging has been opened. These micro-organisms are likely to cause infections.

Therapy:

- For external use only.
- Chlorhexidine diacetate solution 1% is used for the disinfection of intact skin, for example prior to surgical procedures. For the disinfection of wounds, a more diluted solution (0.1% chlorhexidine diacetate) is preferred. Chlorhexidine is not active against bacterial spores and viruses, but iodine is. Therefore, iodine preparations are often preferred for disinfection.

Dose:

- Prior to surgery: apply the solution to the skin before the operation.
- Disinfection of wounds: apply a 0.1% solution to the wound once or twice daily.

Instructions for use:

- Prior to surgery: the chlorhexidine solution 1% is used on intact skin. Wash the skin thoroughly and apply the solution to the skin.
- Disinfection of wounds: clean the wound carefully. Chlorhexidine is inactivated by wound debris and blood. Apply the solution to the wound with a sterile dressing.
- Use the solution within 24 hours after first opening the container. Discard any remaining solution after this period.

Precautions:

- Chlorhexidine solution 1% should not be allowed to contact the eyes, because it is very irritating. When it occurs accidentally, rinse immediately with a lot of water.
- Chlorhexidine can cause deafness upon contact with the inner parts of the ear. Chlorhexidine solution 1% should only be used for ear infections when the eardrum is intact. This is often difficult to assess.
- Minor wounds healing satisfactory do not need disinfection.

Pregnancy/breast feeding:

- Harmful effects from external use of chlorhexidine solutions have not been reported.

Side effects:

- Irritation and itching may develop. These may aggravate when the skin is exposed to sunlight. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Intoxication:

- After accidental ingestion induce vomiting with syrup of ipecacuanha.

Additional information:

- A 1% chlorhexidine solution is used for the disinfection of intact skin, a 0.1% solution is used for the disinfection of wounds. Such a 0.1% solution is prepared by diluting a 1% solution 1 in 10 with recently boiled and cooled water. Chlorhexidine 0.1% solutions should preferably be sterilised at 121 °C for 15 minutes.
- Chlorhexidine diacetate is available in the form of crystals. This has a better stability than the chlorhexidine digluconate stock solution, and is therefore preferred. Since chlorhexidine digluconate is widely used throughout the industrialised world, and the solutions are equally effective, a disinfectant solution based on the digluconate is also included in the formulary. The solutions are interchangeable. Chlorhexidine dichloride is not soluble enough for the preparation of antiseptic solutions; it should not be used.
- Resistance against chlorhexidine is occasionally seen, especially in *Pseudomonas* species. Solutions should be freshly prepared to prevent growth of such resistant organisms. Alcohol (industrial methylated spirit) in a concentration of more than 7% is used to prevent growth of these organisms in the solution. For adequate protection, add 10% industrial methylated spirit 95%, this is 10 ml of spirit for each 90 ml of chlorhexidine solution. Resistance against iodine has not been reported, this is another reason why iodine solutions are sometimes preferred.
- Unopened sterilised chlorhexidine solutions do not risk getting contaminated with micro-organisms, and can be kept in stock for 3 months.

Chlorhexidine digluconate solution 1%

Contains: 1% chlorhexidine digluconate in water.

Formulation

chlorhexidine digluconate stock solution 20%		5	ml
water	to	100	ml

Preparation:

1. Boil 120 ml water for 1 minute and allow to cool. Use this water for the preparation.
2. Mix the chlorhexidine stock solution with approximately 80 ml of this water.
3. Add enough water to produce 100 ml and mix well.

Packaging:

- Chlorhexidine digluconate solution should be packed in a well closed container. Cork closures should not be used.
- The solution should be freshly prepared, unless sterilised.

Storage:
- Chlorhexidine digluconate solution should preferably be stored in a cool and dark place.
- Chlorhexidine digluconate solution 1% should preferably be used within 2 days. Sterilised solutions should preferably be used within 2 days after first opening. Unopened sterilised solutions and solutions which contain at least 7% alcohol may be kept in store. These should preferably be used within 3 months.
- Expired chlorhexidine solutions are less effective and risk being contaminated with resistant micro-organisms. Contamination with micro-organisms is especially likely to occur after the packaging has been opened. These micro-organisms are likely to cause infections.

Therapy:
- For external use only.
- Chlorhexidine digluconate solution 1% is used for the disinfection of intact skin, for example prior to surgical procedures. For the disinfection of wounds, a diluted solution (0.1% chlorhexidine digluconate) is preferred. Chlorhexidine is not active against bacterial spores and viruses, but iodine is. Therefore, iodine preparations are often preferred.

Dose:
- Prior to surgery: apply the solution to the skin before the operation.
- Disinfection of wounds: apply a 0.1% solution to the wound once or twice daily.

Instructions for use:
- Prior to surgery: the chlorhexidine solution 1% is used on intact skin. Wash the skin thoroughly and apply the solution to the skin.
- Disinfection of wounds: clean the wound carefully. Chlorhexidine is inactivated by wound debris and blood. Apply the solution to the wound with a sterile dressing.
- Use the solution within 24 hours after first opening the container. Discard any remaining solution after this period.

Precautions:
- Chlorhexidine solution 1% should not be allowed to contact the eyes, because it is very irritating. When it occurs accidentally, rinse immediately with a lot of water.
- Chlorhexidine can cause deafness upon contact with the inner parts of the ear. Chlorhexidine solution 1% should only be used for ear infections when the eardrum is intact. This is often difficult to assess.
- Minor wounds healing satisfactory do not need disinfection.

Pregnancy/breast feeding:
- Harmful effects from external use of chlorhexidine solutions have not been reported.

Side effects:
- Irritation and itching may develop. These may aggravate when the skin is exposed to sunlight. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Intoxication:
- After accidental ingestion induce vomiting with syrup of ipecacuanha.

Additional information:

- A 1% chlorhexidine solution is used for the disinfection of intact skin, a 0.1% solution is used for the disinfection of wounds. Such a 0.1% solution is prepared by diluting a 1% solution 1 in 10 with recently boiled and cooled water. Chlorhexidine 0.1% solutions should preferably be sterilised at 121 °C for 15 minutes.
- Chlorhexidine diacetate is available in the form of crystals. This has a better stability than the chlorhexidine digluconate stock solution, and is therefore preferred. The solutions are interchangeable. Chlorhexidine dichloride is not soluble enough for the preparation of antiseptic solutions; it should not be used.
- Resistance against chlorhexidine is occasionally seen, especially in *Pseudomonas* species. Solutions should be freshly prepared to prevent growth of such resistant organisms. Alcohol (industrial methylated spirit) in a concentration of more than 7% is used to prevent growth of these organisms in the solution. For adequate protection, add 10% industrial methylated spirit 95%, this is 10 ml of spirit for each 90 ml of chlorhexidine solution. Resistance against iodine has not been reported, this is another reason why iodine solutions are sometimes preferred.
- Unopened sterilized chlorhexidine solutions do not risk getting contaminated with micro-organisms. They can be kept in stock for 3 months.

Dithranol cream

anthralin cream

Contains: 1% dithranol in basic cream

Formulation

dithranol	1	g
ascorbic acid	0.1	g
salicylic acid	1	g
basic cream	98	g

Preparation:

1. Mix the salicylic acid, ascorbic acid and dithranol.
2. Triturate this mixture carefully with approximately 2 g basic cream until homogeneous.
3. Add the rest of the basic cream gradually and mix after each addition until homogeneous.

Packaging:

- Dithranol cream should be packed in a well closed, airtight container, which prevents evaporation of water and contamination with micro-organisms, and protects the cream from exposure to light. The packaging should allow stirring of the cream. Dithranol cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.

– When inhomogeneous, dithranol cream should be mixed until homogeneous before dispensing from stock.

Storage:
– The cream should be stored in a cool and dark place at a temperature below 25 °C.
– The cream should preferably be used within 2 months.
– Degraded dithranol creams show a pink to slightly purple discolouration. Such degraded creams are less effective or ineffective.
– Expired creams may be less effective and risk being contaminated with micro-organisms causing infections.
– Dithranol cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
– If the container is not closed properly, water may evaporate during storage. This results in an emulsifying ointment type preparation with a dithranol content between 1 and 2%.

Therapy:
– For external use only.
– Dithranol preparations are used for the treatment of psoriasis. Dithranol cream is a water washable preparation and is therefore suitable for hairy parts of the skin.
– The cream is somewhat less effective, but better tolerated than the ointment.

Dose:
– Apply once daily before going to bed.

Instructions for use:
– Wash the skin carefully.
– When inhomogeneous, mix the cream before use. Apply the cream in a thin layer to the affected skin only. Rub the cream gently into the skin. Avoid applying the cream to surrounding healthy skin. Adjacent healthy skin can be protected with petrolatum. Wash the hands after application.
– In the morning, remove the cream by washing with water only. Many soaps cause excessive staining. Only after all the cream has been removed with water, wash the skin with water and soap.
– Use the cream for the period the doctor has advised. Do not use past the expiry date, or if the cream shows a marked pink or purple discoloration. Use within 1 month after dispensing.

Precautions:
– Dithranol preparations are irritating to healthy skin. Avoid contact with healthy skin.
– Avoid contact of dithranol cream with the eyes.
– When intense pain or a strange skin reaction develops during the use of dithranol preparations, stop the use of such preparations.
– Dithranol preparations stain the skin, clothes and bedding, especially if alkaline soaps are used in washing.

Pregnancy/breast feeding:
– Adverse reactions resulting from external use of dithranol during pregnancy or breast feeding have not been reported, but can be expected for theoretical reasons because dithranol affects the cell division.

Dithranol was found carcinogenic in animal experiments. Consider the possible risks and the need for treatment carefully during pregnancy or breast feeding. Pregnancy itself may have a beneficial effect on psoriasis.

Side effects:

- Dithranol preparations may produce a burning feeling. This is no reason to stop treatment. Only when intense pain develops, treatment should be stopped.
- Dithranol stains the skin, clothes and bedding.
- Dithranol cream may cause irritation resulting from the dithranol itself, or from inferior qualities of white petrolatum used in the cream. The lanette wax in the basic cream may also cause irritation.
- Sensitisation due to methylparaben may develop but is rare with the concentration used in this cream. Sensitisation may also develop due to the dithranol or to the yellow petrolatum used in the cream. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

- Other dithranol concentrations (between 0.1 and 3%) can be used. Some authors recommend to start with a dithranol preparation with a low concentration, for example 0.1%. This is raised slowly until a satisfactory response is obtained. Keep the amounts of salicylic acid (1g/100g cream) and ascorbic acid (0.1g/100g cream) the same for dithranol preparations with other concentrations.
- Ascorbic acid and salicylic acid are added to the preparation to prevent rapid degradation of dithranol. Without both ingredients, the cream has a maximum shelf life of 1 week.
- More information on the preparation and alternative starting materials is found in the monograph on basic cream.
- Dithranol can also be incorporated in either petrolatum or emulsifying ointment. Dithranol in petrolatum is occlusive and less well tolerated.
- Many soaps, in particular alkaline soaps, cause excessive staining when used to wash away dithranol from the skin. Non-alkaline soaps cause less staining.

Dithranol ointment

anthralin ointment

Contains: 1% dithranol and 0.5% salicylic acid in emulsifying ointment.

Formulation

dithranol	1	g
salicylic acid	0.5	g
emulsifying ointment	98.5	g

Preparation:

1. Mix the salicylic acid and the dithranol.
2. Triturate the mixture carefully with approximately 2 g emulsifying ointment and mix until homogeneous.
3. Add the rest of the emulsifying ointment gradually and mix after each addition until homogeneous.

Packaging:

- Dithranol ointment should be packed in a well closed airtight container, which protects the ointment from exposure to light.
- Dithranol ointment should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.

Storage:

- Dithranol ointment should preferably be stored in a cool and dark place.
- Dithranol ointment should preferably be used within 3 months.
- Degraded dithranol ointment shows a pink or purple discolouration. Expired ointment without signs of discolouration can still be used. Degraded ointment is less effective.

Therapy:

- For external use only.
- Dithranol preparations are used for the treatment of psoriasis. Dithranol ointment can be washed away and is therefore suitable for hairy parts of the skin.
- The cream is somewhat less effective, but better tolerated than the ointment.

Dose:

- Apply once daily before going to bed.

Instructions for use:

- Wash the skin carefully.
- Apply the ointment in a thin layer to the affected skin only. Avoid applying the ointment to surrounding healthy skin. Adjacent healthy skin can be protected with petrolatum. Wash the hands after application.
- In the morning, remove the ointment by washing with water and soap. Many soaps cause excessive staining.

– Use the ointment for the period the doctor has advised. Do not use past the expiry date, or if the ointment shows a marked pink or purple discoloration. Use within 1 month after dispensing.

Precautions:
– Dithranol preparations are irritating to healthy skin. Avoid contact with healthy skin.
– Avoid contact of dithranol ointment with the eyes.
– When intense pain or a strange skin reaction develops during the use of dithranol preparations, stop using such preparations.
– Dithranol preparations stain the skin, clothes and bedding, especially when alkaline soaps are used in washing.

Pregnancy/breast feeding:
– Adverse reactions resulting from external use of dithranol during pregnancy or breast feeding have not been reported, but can be expected for theoretical reasons because dithranol affects the cell division. Dithranol was found carcinogenic in animal experiments. Consider the possible risks and the need for treatment carefully during pregnancy or breast feeding. Pregnancy itself may have a beneficial effect on psoriasis.

Side effects:
– Dithranol preparations may produce a burning feeling. This is no reason to stop treatment. Only when intense pain develops, treatment should be stopped.
– Dithranol stains the skin, clothes and bedding.
– Dithranol ointment may cause irritation resulting from the dithranol itself, or from inferior qualities of white petrolatum used in the ointment. The lanette wax used in the vehicle may also cause irritation.
– Sensitisation may develop due to the dithranol or to the yellow petrolatum used in the ointment. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

– Other dithranol concentrations (between 0.1 and 3%) can be used. Some authors recommend to start with a dithranol preparation with a low concentration, for example 0.1%. This is raised slowly until a satisfactory response is obtained. Keep the amount of salicylic acid the same (0.5g/100g ointment) for dithranol preparations with other concentrations.
– The formula is based on the formula of emulsifying ointment. More information is found in the monograph on emulsifying ointment.
– Ascorbic acid is added to the preparation to prevent rapid degradation of dithranol. Without ascorbic acid, the ointment should preferably be used within 1 week and should be kept cool.
– Dithranol can also be incorporated in petrolatum. In this case it is advisable to add 2% salicylic acid to the vehicle before adding the dithranol, to prevent its rapid degradation. An ointment with petrolatum is more occlusive and not recommended.
– Many soaps, especially alkaline soaps, cause excessive staining when used to wash dithranol away from the skin. Non-alkaline soaps cause less staining.

Emulsifying ointment

Contains: 30% lanette wax, 25% liquid paraffin and 45% petrolatum.

Formulation

lanette wax	30	g
liquid paraffin	25	g
petrolatum	45	g

Preparation:

1. Melt all ingredients together over gentle heat.
2. Stir gently until cold.

Packaging:

- The ointment should be packed in a container which allows stirring of the ointment. Emulsifying ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
- When inhomogeneous, emulsifying ointment should be mixed until homogeneous before dispensing from stock.

Storage:

- Emulsifying ointment should preferably be stored below 25 °C.
- Emulsifying ointment should preferably be used within 2 years.
- Expired ointment may show a changed consistency. It may still be used as long as the consistency remains satisfactory.
- Emulsifying ointment may get inhomogeneous at temperatures higher than 25 °C.
- Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:

- For external use only.
- Emulsifying ointment is a fatty ointment base used for various preparations. It is easily washed away with water and is suitable for hairy parts of the skin.
- Emulsifying ointment has a mild occlusive effect and is used as emollient and mild moisturizer, for instance in the management of dry skin in leprosy.
- Do not use past the expiry date. Use within 3 months after dispensing.

Dose:

- As an emollient: apply in a thin layer several times daily.

Instructions for use:

- When inhomogeneous, mix the ointment before use. The ointment should be applied in a thin layer. When using it as an emollient and moisturizer, hydrate the skin by keeping it wet for 10 to 15 minutes, for example by taking a bath, before applying the ointment.

Precautions:

– The ointment should be applied in a thin layer. An occlusive effect may result from thick layers of emulsifying ointment. This may cause gross hydration of the skin and subsequent complications such as secondary infections.

Pregnancy/breast feeding:

– Harmful effects from external use of emulsifying ointment have not been reported.

Side effects:

– Yellow petrolatum may cause sensitisation reactions. Sensitisation reactions due to white petrolatum are rare. White petrolatum of inferior quality may cause irritation of the skin. Skin irritation due to lanette wax has been described. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

– This preparation is analogous to the emulsifying ointment of the *British Pharmacopoeia*.
– When liquid paraffin is unavailable, the ointment can be prepared with petrolatum 70% and lanette wax 30%. This has only a limited effect on consistency and stability. The reverse is not possible, an ointment with 70% liquid paraffin and 30% lanette wax has poor physical stability.
– For a number of indications an alternative vehicle is petrolatum with 10% wool fat. This has some drawbacks. The ointment is far more sensitising, more occlusive, less stable, and cannot be washed away as easily as emulsifying ointment. It is therefore unsuitable for hairy parts of the skin.
– Petrolatum alone can be used as a vehicle but it is not water washable and very occlusive. Occlusion leads to gross hydration of the skin, which may result in secondary skin infections.

Gentian violet solution 0.5%

methylrosanilinium chloride solution, crystal violet solution.

Contains: 0.5% gentian violet in water.

Formulation

gentian violet	0.5	g
water	100	ml

Preparation:

1. Boil 120 ml water for 1 minute and allow to cool.
2. Dissolve the gentian violet in 100 ml of this water.
3. Check for undissolved crystals on the bottom of the flask. If dissolution is incomplete, continue shaking. Gentle heat may be used.

Packaging:

- Gentian violet solution should be packed in well closed containers.
- When gentian violet solution is dispensed from stock, complete dissolution should be carefully checked by looking for undissolved crystals on the bottom. When crystals are present, shake until they have completely dissolved.
- One patient needs 10 to 100 ml, depending on localisation and size of the infection. To reduce the risk of bacterial contamination, the preparation should be dispensed in a supply sufficient for 1 week.

Storage:

- The solution should be stored at room temperature. The optimal storage temperature is between 15 and 30 °C. When stored cooler than 15 °C, gentian violet may crystallize from the solution.
- The solution should preferably be used within 3 months. After opening the solution is readily contaminated with micro-organisms which may cause infections. Therefore, the product should not be used longer than 1 week after first opening.
- Expired solutions may be contaminated with resistant micro-organisms causing infections.
- If the container is not closed properly, water may evaporate during storage. This results in a more concentrated solution which may cause more side effects.

Therapy:

- Gentian violet solution is for external use only.
- Gentian violet has good antimicrobial activity against *Candida* species. Gentian violet solution is used for the treatment of *Candida* infections of the skin and mouth. *Candida* infections of the vagina can also be treated with gentian violet, but other pharmaceutical forms should be chosen, for example vaginal tablets.
- Gentian violet has antimicrobial activity against a number of bacteria, particularly Gram positive organisms. It may therefore be used as a paint once daily for ulcers, e.g., in leprosy. For the treatment of severe or deep infections systemic antibiotics are required.

Dose:
– The solution should be applied to the affected parts of the skin or the oral mucosa once or twice daily for 3 days, or until the disease has markedly improved.

Instructions for use:
– Skin infections: clean the skin with water and soap. Apply gentian violet solution to the affected parts of the skin only. Leave the affected parts of the skin exposed to the air. Do not cover with bandages. Clean clothes and bed sheets regularly.
– Oral infections: apply the solution to the affected parts. Avoid contact with healthy parts of the mucosa. Gentian violet solution should not be swallowed. Children should be turned face down after application to avoid swallowing.
– Ulcers: remove any necrotic tissue and callous skin around the fissure mechanically with a sterile instrument. Paint the depth of the crack with gentian violet solution once daily. Cover with a loose bandage.
– Use gentian violet solution within 1 week after dispensing, and discard any remaining solution.

Precautions:
– The solution stains clothes and bedding. Stains are difficult to remove with water and soap. From some materials they can be removed with alcohol.
– The solution stains the skin. Staining on damaged skin may be permanent (tattooing). The solution should therefore not be used in the face and preferably not on open wounds.
– Undissolved gentian violet crystals are very irritating. It is therefore important to check for complete dissolution before dispensing or use.

Pregnancy/breast feeding:
– In animal experiments a mutagenic effect has been found. In humans, harmful effects from gentian violet have been reported. Avoid using gentian violet during pregnancy.

Side effects:
– Irritation of the skin or mucosa may occur.
– Necrotic skin reactions are reported after using gentian violet solutions of 1% or more. Such reactions will be rare with the 0.5% solution. When they develop stop using the preparation and consult a doctor.

Intoxication:
– After accidental ingestion, gentian violet can damage the gullet and stomach. Request for medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

Additional information:
– Gentian violet solution is often prescribed as a 1% solution. The 0.5% is as effective as the 1% solution, and less irritating, safer and cheaper.

Hydrocortisone cream 1%

hydrocortisone acetate cream.

Contains: 1% hydrocortisone acetate in basic cream.

Formulation

hydrocortisone acetate	1	g
basic cream	99	g

Preparation:

1. Grind the hydrocortisone acetate. When sieves are available, sieve the hydrocortisone acetate, preferably through a 90 µm sieve.
2. Triturate the hydrocortisone acetate carefully with approximately 1 g basic cream until homogeneous.
3. Add the rest of the cream gradually and mix until homogeneous.

Packaging:

- Hydrocortisone cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms, and protects the cream from exposure to light. The container should allow stirring of the cream. The cream should not be stored in collapsible tubes when the storage temperature may exceed 40 °C.
- When inhomogeneous, hydrocortisone cream should be mixed until homogeneous before dispensing from stock.

Storage:

- Hydrocortisone cream should preferably be stored in a cool and dark place. It should be kept at a temperature below 40 °C, or even better, below 30 °C.
- The cream should preferably be used within 3 weeks. If the cream is exposed to temperatures higher than 40 °C, it should be used within 1 week.
- Expired creams may be less effective and risk being contaminated with micro-organisms causing infections.
- The cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
- If the container is not closed properly, water may evaporate during storage. This results in an emulsifying ointment type preparation with a hydrocortisone content between 1 and 2%.

Therapy:

- For external use only.
- Hydrocortisone cream has general anti-inflammatory properties. It is used for the treatment of many skin diseases, for example eczema. Treatment is only symptomatic.
- Hydrocortisone cream is a water washable preparation and is suitable for hairy parts of the skin. Whether the cream or ointment is preferred in the local formulary, depends on the local situation.

Dose:
- Apply the cream to a maximum of 3 times daily in a thin layer.
- Do not use more than 50 g cream per week, unless on doctor's instructions.

Instructions for use:
- When inhomogeneous, mix the cream before use.
- After application of hydrocortisone cream do not cover the skin with wrappings or bandages, unless on doctor's instructions.
- Do not use past the expiry date. Do not use for more than 1 month unless on doctor's instructions. Use within 1 week after dispensing.

Precautions:
- Do not use hydrocortisone cream on infections, as the corticosteroid may worsen them.
- Apply hydrocortisone cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Hydrocortisone cream gives symptomatic relief. When treatment is stopped the disease may return.
- Hydrocortisone cream should not be used for prolonged periods of time unless on doctor's advice.
- Avoid contact of hydrocortisone cream with the eyes.
- In children, growth retardation may result from prolonged use of corticosteroids on the skin. Regular checks on both length and weight is recommended for children during treatment with corticosteroids on the skin, especially when large quantities are used, or use during prolonged periods of time.

Pregnancy/breast feeding:
- Corticosteroids in high systemic doses were teratogenic in animal experiments. Corticosteroids applied to the skin are absorbed to some extent, pass the placenta and may influence the unborn child. However, harmful effects from external use of class I corticosteroids, such as hydrocortisone, have not been reported. Carefully evaluate the need for treatment during pregnancy.
- Corticosteroids are excreted in breast milk, but adverse effects in the baby resulting from the mother's external use of class I corticosteroids, such as hydrocortisone, have not been reported. Carefully evaluate the need for treatment during breast feeding.

Side effects:
- Hydrocortisone cream masks infections.
- Hydrocortisone cream may delay the healing of damaged skin.
- Local side effects of corticosteroids used on the skin include irritation, an itching or burning sensation, and depigmentation. After prolonged use of corticosteroid preparations thinning of the skin may result. These effects most frequently occur in the face, on hairy parts of the skin, and in the genital region.
- Systemic side effects due to local use of hydrocortisone cream are uncommon, but may be very serious. They include suppression of the synthesis of corticosteroids in the adrenal glands.
- Sensitisation reactions due to hydrocortisone are rare, but have been described. Methylparaben, the preservative used in the cream, may cause sensitisation in rare cases. Yellow petrolatum may also cause sensitisation reactions. The lanette wax used in the cream may cause irritation of the skin, but such reactions are rare. Inferior qualities of white petrolatum may also cause irritation. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Additional information:

- Lower concentrations of hydrocortisone are obtained by further dilution of the preparation with basic cream.
- If basic cream is unavailable, hydrocortisone ointment can be used instead. For other alternative vehicles see the monograph on hydrocortisone ointment.
- When larger quantities of hydrocortisone cream are prepared for stock storage, a freshly prepared basic cream should be used.

Hydrocortisone ointment 1%

hydrocortisone acetate ointment.

Contains: 1% hydrocortisone acetate in emulsifying ointment.

Formulation

hydrocortisone acetate	1	g
emulsifying ointment	99	g

Preparation:

1. Grind the hydrocortisone acetate. When sieves are available, sieve the hydrocortisone acetate, preferably through a 90 µm sieve.
2. Triturate the hydrocortisone acetate carefully with about 1 g emulsifying ointment until homogeneous.
3. Add the rest of the ointment gradually and mix until homogeneous.

Packaging:

- Hydrocortisone ointment should be packed in a well closed container protecting the ointment from exposure to light. The container should allow stirring of the ointment. Hydrocortisone ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
- When inhomogeneous, hydrocortisone ointment should be mixed until homogeneous before dispensing from stock.

Storage:

- Hydrocortisone ointment should preferably be stored in a cool and dark place. It should be kept at a temperature below 40 °C, or even better, below 25 °C.
- The ointment should preferably be used within 2 months. If the ointment is exposed to temperatures higher than 40 °C it should be used within 2 weeks.
- Expired hydrocortisone ointment may be less effective.
- Hydrocortisone ointment may get inhomogeneous at temperatures higher than 25 °C. Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:

- For external use only.
- Hydrocortisone ointment has general anti-inflammatory properties. It is used for the treatment of many skin diseases, for example eczema. Treatment is only symptomatic. Hydrocortisone ointment is water washable and suitable for hairy parts of the skin. Whether the cream or ointment is preferred in the local formulary, depends on the local situation.

Dose:

- Apply the ointment to a maximum of 3 times daily in a thin layer.
- Do not use more than 50 g ointment per week, unless on doctor's instructions.

Instructions for use:

- When inhomogeneous, mix the ointment before use.
- After application of hydrocortisone ointment, do not cover the skin with wrappings or bandages, unless on doctor's instructions.
- Do not use past the expiry date. Do not use for more than 1 month unless on doctor's instructions. Use within 2 weeks after dispensing.

Precautions:

- Do not use hydrocortisone ointment on infections, as the corticosteroid may worsen them.
- Apply hydrocortisone ointment in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Hydrocortisone ointment gives symptomatic relief. When treatment is stopped the disease may return.
- Hydrocortisone ointment should not be used for prolonged periods of time unless on doctor's advice.
- Avoid contact of hydrocortisone ointment with the eyes.
- In children, growth retardation may result from prolonged use of corticosteroids on the skin. Regular checks on both length and weight is recommended for children during treatment with corticosteroids on the skin, especially when large quantities are used, or use during prolonged periods of time.

Pregnancy/breast feeding:

- Corticosteroids in high systemic doses were teratogenic in animal experiments. Corticosteroids applied to the skin are absorbed to some extent, pass the placenta and may influence the unborn child. However, harmful effects from external use of class I corticosteroids, such as hydrocortisone, have not been reported. Carefully evaluate the need for treatment during pregnancy.
- Corticosteroids are excreted in breast milk, but adverse effects in the baby resulting from the mother's external use of class I corticosteroids, such as hydrocortisone, have not been reported. Carefully evaluate the need for treatment during breast feeding.

Side effects:

- Hydrocortisone ointment masks infections.
- Hydrocortisone ointment may delay the healing of damaged skin.
- Local side effects of corticosteroids used on the skin include irritation, an itching or burning sensation, and depigmentation. After prolonged use of corticosteroid preparations thinning of the skin may occur. These effects most frequently occur in the face, on hairy parts of the skin, and in the genital region.
- Systemic side effects due to local use of hydrocortisone ointment are uncommon, but may be very serious. They include suppression of the synthesis of corticosteroids in the adrenal glands.

– Sensitisation reactions due to hydrocortisone are rare, but have been described. Sensitisation reactions may also be due to yellow petrolatum. Irritation reactions to lanette wax or inferior qualities of white petrolatum may occur but are rare. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Additional information:

– Lower concentrations of hydrocortisone are obtained by dilution of the preparation with emulsifying ointment.
– When emulsifying ointment is unavailable, petrolatum with 10% wool fat may be used. This gives a non-washable preparation with a higher sensitisation risk. Alternatively, petrolatum alone may be used, but this will result in a less active and more occlusive preparation.
– When larger quantities of hydrocortisone ointment are prepared for stock storage, a freshly prepared emulsifying ointment should preferably be used.

Industrial methylated spirit 70%

alcohol 70%

Contains: 70 % industrial methylated spirit in water.

Formulation

industrial methylated spirit 95%		74	ml
water	to	100	ml

Preparation:

1. Add enough recently boiled and cooled water to the spirit to produce 100 ml solution.
2. Mix well and allow to cool.
3. Make up to exactly 100 ml with recently boiled and cooled water.

Packaging:

– Industrial methylated spirit 70% should be packed in a well closed container.

Storage:

– Industrial methylated spirit 70% should preferably be stored cool.
– Industrial methylated spirit 70% is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where industrial methylated spirit is stored.
– Industrial methylated spirit 70% should preferably be used within 3 months.

– Expired industrial methylated spirit 70% may have a lower alcohol content due to evaporation of alcohol. The alcohol content is checked by weighing exactly 100 ml of the spirit. The weight should read 88.7 g. A higher weight indicates evaporation of alcohol.

Therapy:

– For external use only.
– Industrial methylated spirit has drying, antiseptic and slightly astringent properties. It is used as a disinfectant for smooth surfaces, particularly in hospitals. For disinfection of the skin prior to surgery, iodine tincture or solution is preferred, or, alternatively, chlorhexidine solution may be used.

Precautions:

– Industrial methylated spirit is highly flammable.

Pregnancy/breast feeding:

– Harmful effects from external use of industrial methylated spirit have not been reported.

Side effects:

– Irritation reactions have been seen occasionally. Dermatitis may occur when less suitable qualities of industrial methylated spirit are used on the skin. When irritation or sensitisation reactions develop, stop using the preparation and do not use it again.

Intoxication:

– Industrial methylated spirit should only be used externally. After ingestion this type of alcohol is toxic and may cause blindness. It should never be used for oral preparations.
– After accidental ingestion of large quantities of industrial methylated spirit request for medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha and bring a 5% solution of sodium bicarbonate in the stomach.

Additional information:

– 70% industrial methylated spirit is a more potent disinfectant than either higher concentrated, or more diluted solutions. This strength should therefore be used for disinfection and antiseptic purposes.
– When 95% industrial methylated spirit is unavailable, but spirits with another strength are, the required quantity of spirit is calculated with the following formula: amount needed = 100 x strength wanted/ strength available. For 'strength wanted' fill in 70%. For 'strength available' fill in the strength of the industrial methylated spirit in stock. An example: your industrial methylated spirit has a strength of 90%. You should dilute 100 x 70/90 ml = 78 ml with water to 100 ml.

Iodine solution 2%

iodine topical solution

Contains: 2% iodine in water

Formulation

iodine	2	g
potassium iodide	2.5	g
water	to 100	ml

Preparation:

1. Iodine reacts with a great number of substances. Metallic or plastic utensils should not be used in the preparation of iodine solution. Glass and earthenware are appropriate.
2. Boil sufficient water for 1 minute and allow to cool. Use this water for the preparation.
3. Dissolve the potassium iodide in 5 ml water.
4. Dissolve the iodine in this solution.
5. Add enough recently boiled and cooled water to produce 100 ml solution.

Packaging:

- Iodine solution should be packed in well closed, airtight containers made of glass or earthen ware. Metallic closures are unsuitable. The container should prevent evaporation of iodine and water, and it should provide protection from exposure to light.
- Mix the iodine stock solution before dispensing.

Storage:

- Iodine solution should be kept below 35 °C. The solution should be protected from exposure to light.
- Iodine solution should be used within 3 months.
- During storage, evaporation of water and iodine may occur, and iodine may degrade. This will probably result in a solution with a higher iodine concentration.
- Expired iodine solution may be less effective.

Therapy:

- For external use only.
- Iodine has a strong antiseptic activity against all micro-organisms, including bacterial spores and viruses. It is used for disinfection of intact skin and for wounds. For disinfection of intact skin, iodine tincture is preferred above iodine solution, because it has a stronger and quicker onset of action. For wound disinfection the less irritating iodine solution is preferred; a quick onset of action is not required in this case.

Dose:

- Disinfection of intact skin: apply the solution to the skin several minutes before the operation.
- Disinfection of wounds: apply the solution to the wound once or twice daily.

Instructions for use:
- Disinfection of intact skin: wash the skin carefully and apply the solution to the skin several minutes before the operation.
- Disinfection of wounds: clean the wound carefully. Iodine is inactivated by wound debris, blood and pus. After thorough cleaning apply the solution with a sterile dressing. Iodine treated skin should not be covered with a tight bandage.
- Do not use past the expiry date.

Precautions:
- Minor wounds healing satisfactory do not need disinfection.
- Iodine treated skin should not be covered with tight or occlusive bandages, because this causes irritation and blistering of the skin.
- Iodine solution is very irritating to the eyes. After accidental contact, rinse the eyes immediately with a lot of water.
- Iodine is absorbed to some extent, even through healthy, intact skin. After absorption, it interferes with the thyroid function. Iodine solution should therefore only be used with great care in patients with disorders of the thyroid gland (goitre etc.).

Pregnancy/breast feeding:
- Iodine is absorbed to some extent, even through healthy, intact skin. It passes the placenta and interferes with the thyroid function of the unborn child. Iodine preparations should therefore be avoided during pregnancy, unless there is a pressing necessity. Consider chlorhexidine as an alternative.
- Iodine is excreted in breast milk. It may interfere with the thyroid function of the newborn child. Avoid using iodine during breast feeding. Consider chlorhexidine as an alternative.

Side effects:
- Iodine is an irritating and sensitising substance.
- Iodine and iodides may cause acne-like skin eruptions, bullous eruptions and tumour-like lesions.
- Iodine is absorbed to some extent, even through healthy, intact skin. After chronic use on large parts of the body, this may result in a characteristic pattern of systemic side effects called iodism. Iodism is characterized by mental depression, nervousness, insomnia, sexual impotence and thyroid disfunctioning. Children are more vulnerable to developing iodism than adults.

Intoxication:
- Iodine is corrosive and toxic when ingested. After accidental ingestion request for medical advice. While waiting for a doctor, give milk and starch first, and then induce vomiting with syrup of ipecacuanha. When starch is unavailable, sodium thiosulphate solution can be used instead.

Additional information:
- Povidone iodine solution is often preferred over iodine solution, as it is better tolerated.
- This formulation is based on iodine topical solution as included in the *United States Pharmacopeia*.
- Intact skin disinfection and wound care each need a different approach. In the first case, a rapid action is needed and irritation is not a problem. But in the second case, irritation and a delay in wound healing are important, while rapid action is less so because the contact time is much longer. For intact skin disinfection

iodine tincture is preferred. This is an irritating preparation, but it is very effective and has a rapid action. For wound care, the slower acting, but better tolerated, iodine solution is preferred.
- Potassium iodide is preferred over sodium iodide for this preparation because potassium iodide is already included in the WHO Essential Drugs List for other indications. However, sodium iodide (in the same amount) can be used as well.
- In an aqueous solution 2% iodine is generally considered effective. Higher concentrations are not necessary, lower concentrations may be less effective. If alcohol is added, lower iodine concentrations are possible (see the monograph on iodine tincture).

Iodine tincture 2%

iodine alcoholic solution

Contains: 2% iodine in an approximately 50% alcoholic solution

Formulation

iodine		2	g
potassium iodide		2.5	g
industrial methylated spirit 95%		50	ml
water	to	100	ml

Preparation:

1. Iodine reacts with a great number of substances. Metallic or plastic utensils should not be used in the preparation of iodine tincture. Glass and earthenware are appropriate.
2. Boil sufficient water for 1 minute and allow to cool. Use this water for the preparation.
3. Dissolve the potassium iodide in 5 ml water.
4. Dissolve the iodine in this solution.
5. Add the industrial methylated spirit to this solution. Iodine forms irritating substances with acetone and other ketones. The industrial methylated spirit used for the preparation of iodine tincture should be free from acetone and other ketones.
6. Add enough recently boiled and cooled water to produce 100 ml tincture.

Packaging:

- Iodine tincture should be packed in well closed, airtight containers made of glass or earthen ware. Metallic closures are unsuitable. The container should prevent evaporation of iodine, alcohol and water, and it should provide protection from exposure to light.
- Mix the iodine tincture before dispensing from stock.

Storage:
- Iodine tincture should be protected from exposure to light.
- Iodine tincture should be used within 3 months.
- During storage, evaporation of water, alcohol and iodine may occur, and iodine may degrade. This results in a tincture with a higher or lower iodine concentration.
- Expired iodine tincture may be less effective and more irritating.

Therapy:
- For external use only.
- Iodine has a strong antiseptic activity against all micro-organisms, including bacterial spores and viruses. It is used for disinfection of intact skin and for wounds. For disinfection of intact skin, iodine tincture is preferred above iodine solution, because it has a stronger and quicker onset of action. For wound disinfection the less irritating iodine solution is preferred, a quick onset of action is not required.

Dose:
- Disinfection of intact skin: apply the tincture to the skin several minutes before the operation.
- Disinfection of wounds: apply the tincture to the wound once or twice daily.

Instructions for use:
- Disinfection of intact skin: wash the skin carefully and apply the tincture to the skin several minutes before the operation.
- Disinfection of wounds: clean the wound carefully. Iodine is inactivated by wound debris, blood and pus. After thorough cleaning apply the tincture with a sterile dressing. Iodine treated skin should not be covered with a tight bandage.
- Do not use past the expiry date.

Precautions:
- Minor wounds healing satisfactory do not need disinfection.
- Iodine treated skin should not be covered with tight or occlusive bandages, because this causes irritation and blistering of the skin.
- Iodine tincture is very irritating to the eyes. After accidental contact, rinse the eyes immediately with a lot of water.
- Iodine is absorbed to some extent, even through healthy, intact skin. After absorption, it interferes with the thyroid function. Iodine tincture should therefore only be used with great care in patients with disorders of the thyroid gland (goitre etc.).
- Iodine forms irritating products with acetone and other ketones which are often present in industrial methylated spirit. The spirit used for iodine tincture should be free of such ketones. A special "acetone-free" industrial methylated spirit should be used.

Pregnancy/breast feeding:
- Iodine is absorbed to some extent, even through healthy, intact skin. It passes the placenta and interferes with the thyroid function of the unborn child. iodine preparations should therefore be avoided during pregnancy, unless there is a pressing necessity. Consider chlorhexidine as an alternative.

– Iodine is excreted in breast milk. It may interfere with the thyroid function of the newborn child. Avoid using iodine during breast feeding. Consider chlorhexidine as an alternative.

Side effects:
– Iodine is an irritating and sensitising substance.
– Iodine and iodides may cause acne-like skin eruptions, bullous eruptions and tumour-like lesions.
– Iodine is absorbed to some extent, even through healthy, intact skin. After chronic use on large parts of the body, this may result in a characteristic pattern of systemic side effects called iodism. Iodism is characterized by mental depression, nervousness, insomnia, sexual impotence and thyroid disfunctioning. Children are more vulnerable to developing iodism than adults.

Intoxication:
– Iodine is corrosive and toxic when ingested. After accidental ingestion, request for medical advice. While waiting for a doctor, give milk and starch first and then induce vomiting with syrup of ipecacuanha. After vomiting, bring a sodium bicarbonate solution in the stomach. When starch is unavailable, sodium thiosulphate solution can be used instead.

Additional information:
– Povidone iodine is generally preferred over iodine tincture, because it is better tolerated.
– This formulation is based on iodine tincture as included in the *United States Pharmacopeia*.
– Intact skin disinfection and wound care each need a different approach. In the first case, a rapid action is needed and irritation is not a problem. But in the second case, irritation and a delay in wound healing are important, while rapid action is less so because the contact time is much longer. For intact skin disinfection iodine tincture is preferred. This is an irritating preparation, but it is very effective and has a rapid action. For wound care, the slower acting, but better tolerated, iodine solution is preferred.
– Potassium iodide is preferred over sodium iodide for this preparation, because potassium iodide is already included in the WHO Essential Drugs List for other indications. However, sodium iodide (in the same amount) may be used as well.
– 2% iodine in 50% spirit is effective. If the strength of the spirit is raised to 70%, the iodine concentration can be lowered to 1%. Alcohol and iodine are thus, in a certain way, interchangeable. Iodine concentrations higher than 2% are not necessary.
– When industrial methylated spirit is unavailable, iodine solution can be used for disinfection of intact skin, but requires longer contact time.

Lindane cream 1%

gammexane cream, hexachlorocyclohexane cream.

Contains: 1% lindane in a water washable cream.

Formulation

lindane		1	g
lanette wax		14	g
liquid paraffin		8	g
methylparaben		0.15	g
water	to	100 g	

Preparation:

1. Melt together the lanette wax and the liquid paraffin over gentle heat to approximately 70 °C and mix.
2. Dissolve the lindane in this mixture.
3. Boil 75 ml water for 1 minute and dissolve the methylparaben in this water. Allow the solution to cool to approximately 70 °C.
4. Add the paraffin/lanette wax mixture to the solution under rapid stirring.
5. Stir gently until cold.
6. Add enough recently boiled and cooled water to produce 100 g cream. Stir until homogeneous.

Packaging:

- Lindane cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms, and protects the cream from exposure to light. The packaging should allow stirring of the cream.
- Lindane cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.
- When inhomogeneous, lindane cream should be mixed until homogeneous before dispensing from stock.
- One patient needs approximately 50 g of this cream.

Storage:

- The cream should preferably be stored in a dark place below 40 °C.
- The cream should preferably be used within 3 months.
- Expired creams risk being contaminated with micro-organisms causing infections.
- Lindane cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
- If the container is not closed properly, water may evaporate during storage. This results in an emulsifying ointment type preparation with a lindane content between 1 and 4%. Such creams may cause toxic effects and should therefore not be used.

Therapy:

- For external use only.

– Lindane cream is used for the treatment of scabies and lice infestations. It is water washable and is suitable for hairy parts of the skin. It is effective after a single application. Due to environmental concerns lindane is no longer available in many countries. Benzyl benzoate is the first alternative, but sulphur 10% can also be used. For pregnant women and children under the age of 3 some authors do not recommend lindane, and prefer benzyl benzoate emulsion or sulphur cream or ointment.

Dose:
– Scabies: apply the cream from the neck down to the whole body only once.
– Lice: apply the cream to the affected and adjacent parts only once.

Instructions for use:
– When inhomogeneous, mix the cream before use.
– Scabies: apply the cream in a thin layer from the neck down to the whole body and rub it into the skin. Make sure the cream gets into contact with the whole body, including skin folds. Wash hands after application. Allow the cream to remain on the skin for 24 hours. Wash the body thoroughly with water and soap. Wash all clothes, bed sheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water, to prevent reinfestation. It is also recommended to shake out blankets and outer wear. Discard any unused cream, preferably by returning it to the dispensary.
– Itch may persist for weeks after all the mites have been killed. Do not repeat lindane treatment but use some calamine lotion to relieve the itch.
– Lice: rub the cream into all affected hairy areas and allow to remain for 24 hours. Take care to avoid all contact with the eyes. Wash off thoroughly and comb the hair with a fine comb to remove dead lice. Wash all bed sheets, pillowcases and clothes, preferably in hot or boiling water and shake out blankets and outer wear. Discard any unused cream, preferably by returning it to the dispensary.

Precautions:
– Lindane is a toxic substance. Misuse may result in serious intoxications. When using lindane follow these rules:
  • Do not wash the skin or take a bath immediately before application;
  • Do not repeat lindane treatment within 1 month or more than twice a year.
  • Lindane cream is more toxic for malnourished people and small children under the age of three. Benzyl benzoate emulsion or sulphur 10% ointment or cream should be used instead.
– Avoid contact with the eyes.
– Lindane cream should not be used by people who have had allergic skin reactions to lindane cream or basic cream.
– Scabies and lice usually affect more members of a household or community. Since treating one of them is a waste of time and money, try to treat all household or community members. As to pubic lice, treat all sexual partners.

Pregnancy/breast feeding:
– In animal experiments a mutagenic effect of lindane has been shown. Lindane is absorbed to some extent after topical application. Therefore, a toxic effect to the unborn child can be expected, but the clinical relevance of this toxicity is still under discussion. Carefully evaluate the need for treatment before using lindane cream during pregnancy, or consider the use of benzyl benzoate as an alternative.
– Small amounts of lindane are excreted in breast milk. The clinical effect of this is probably insignificant. However, carefully evaluate the need for treatment during breast feeding.

Side effects:
- Sensitisation due to methylparaben may occur but is unlikely with the concentration used in this cream.
- Irritation due to lanette wax has been described, but is rare.
- Irritation or sensitisation reactions to lindane are very uncommon after single use. Contact dermatitis may result from repeated use. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Intoxication:
- Lindane has a general toxic effect on the nervous system. After prolonged, extensive use of the cream restlessness, muscle spasms and seizures may occur. Coma and death from respiratory failure may occur. It is important not to overuse lindane cream.
- After ingestion gastric lavage is only of value when undertaken rapidly. Intravenous diazepam is given to treat seizures. Otherwise treatment is supportive, and consists of keeping the patient warm, assisting respiration etc.

Additional information:
- Lindane has become a controversial drug in scabies and lice treatment as it is environmentally unsafe. In our opinion it can still be used and it is at the moment by far the cheapest effective drug for the treatment of scabies. Two of the authors of this book have a vast positive experience with the treatment of scabies with lindane. Proper instruction on the use of the preparation is absolutely necessary.
- This formula has been modified from the formula of the *British Pharmacopoeia* for lindane cream that was first published in the addendum 1977. A preservative is added. When this is dropped, the cream should not be held in store.
- The cream can be prepared with other lindane concentrations as well. For the treatment of lice a 0.4%, or even a 0.1% cream is often used. To prepare such creams use 0.4 g or 0.1 g instead of 1 g lindane for 100 g cream.
- To prepare lindane cream, the oil phase is added to the water phase under rapid stirring. This differs from the usual preparation method for creams. The reason to apply this method for lindane cream is that it ensures a small droplet size and a homogeneous distribution of droplets.
- Non-drug treatment of lice consists of:
  - regular hair combing with a fine comb to remove lice;
  - regular washing of clothes, bed sheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water. It is also recommended to shake out blankets and outer wear.
- In industrialized countries in North America and Europe the scabies mite is occasionally found to be resistant to lindane. Treatment failure is difficult to assess, because the itch persists for some time after all the mites have been killed. In case of a treatment failure, try benzyl benzoate emulsion. Avoid more than two lindane treatments per year.
- Lice may also be resistant to lindane. Try intensive non-drug treatment for resistant lice.
- Lindane has been used in various ointments, such as petrolatum, petrolatum with wool fat, vegetable oils and emulsifying ointment. These vehicles have some occlusive and hydrating effect which can cause more lindane absorption and higher toxicity. In addition, these vehicles are not as easily washed away as the cream. This can cause more absorption because the product remains on the skin for a longer period. It negatively affects the safety of the preparation. Therefore, we strongly advise to use the generally recommended vehicles such as this cream. Lindane cattle dip has also been used for humans. The risks of this kind of preparation are unknown.

Miconazole cream 2%

Contains: 2% miconazole nitrate in a water washable cream.

Formulation

Commercial preparation. Miconazole cream is commercially available under various trade names.

Packaging:

– See product specifications.

Storage:

– See product specifications.
– Expired creams may be less effective and contaminated with micro-organisms causing infections.
– Miconazole cream may get inhomogeneous at higher temperatures. When this happens, the cream should be mixed before dispensing or use.
– If the container is not closed properly, water may evaporate during storage. This results in a preparation with different characteristics.

Therapy:

– For external use only.
– Miconazole cream is a broad spectrum antimycotic preparation. It is used against all superficial skin mycoses, including candidosis. Miconazole cream is water washable and suitable for hairy parts of the skin. Miconazole cream is relatively expensive. For the treatment of superficial mycotic skin infections Whitfield's cream or ointment is preferred. For the treatment of superficial candidosis gentian violet solution is preferred. For pityriasis versicolor sodium thiosulphate is the drug of first choice. If these preparations are ineffective or not well tolerated, miconazole cream is a good alternative.

Dose:

– See product specifications.
– Apply twice daily until the lesions are completely cleared, usually this takes 2 to 5 weeks.

Instructions for use:

– See product specifications.
– Clean the skin with water and soap before application of the cream. Apply the cream in a thin layer to prevent occlusion. Occlusion resulting from thick layers of cream may lead to an exacerbation of the infection. Do not cover with wrappings or bandages.
– Do not use past the expiry date.

Precautions:

– See product specifications.
– Avoid contact of miconazole cream with the eyes.
– Occlusion and hydration favour growth of *Candida* species.

Pregnancy/breast feeding:
- See product specifications.
- Harmful effects from external use of miconazole cream have not been reported.

Side effects:
- Irritation reactions with a burning feeling may develop.
- Sensitisation reactions are rare. If any strange skin reaction occurs, stop using the cream.

Additional information:
Miconazole is incompatible with basic cream and emulsifying ointment. The stability and effectiveness of processing miconazole in basic cream or emulsifying ointment are unknown. Miconazole can be processed in cetomacrogol cream for which a suitable formula is found on www.openapo.info.

Nystatin preparation

Contains: 100.000 units nystatin per gram in a cream or ointment.

Formulation
Commercial preparation. Nystatin is commercially available in various preparations and under various trade names. Both creams and ointments are used, but creams are preferred.

Packaging:
- See product specifications.

Storage:
- See product specifications.
- Nystatin preparations should be stored in a refrigerator.
- Expired nystatin preparations, or nystatin preparations that were kept outside the refrigerator, may be less effective or ineffective, and contaminated with micro-organisms causing infections.
- Nystatin preparations may get inhomogeneous at higher temperatures. When inhomogeneous, they should be mixed before dispensing or use. When nystatin preparations are exposed to temperatures high enough to cause inhomogeneity, the nystatin is most likely to be degraded and the preparation is unreliable. Such preparations should be discarded.

Therapy:

- For external use only.
- Nystatin has a strong fungistatic activity against *Candida* species. Nystatin is an instable drug. It is unsuitable for general use in tropical countries. Candidosis should preferably be treated with gentian violet solution. The next choice is miconazole cream. Nystatin can be useful in well-equipped hospitals with well-functioning refrigerators for storage. The cream is preferred over the ointment because it is less occlusive. Occlusion and hydration create a favourable environment for the growth of *Candida* species and various bacteria.

Dose:

- See product specifications.
- Apply the nystatin preparation twice daily for 2 weeks.

Instructions for use:

- See product specifications.
- Wash the skin carefully with water and soap and allow to dry. Apply the cream or ointment in a thin layer to prevent occlusion. Do not cover with wrappings or bandages.
- Do not use past the expiry date.

Precautions:

- See product specifications.
- Avoid contact of nystatin preparations with the eyes.
- Symptomatic relief usually occurs 1 to 3 days after starting the medication. Treatment should be continued for 2 weeks to prevent recurrences.

Pregnancy/breast feeding:

- See product specifications.
- Harmful effects from external use of nystatin preparations have not been reported.

Side effects:

- See product specifications.
- Irritation and sensitisation are reported but are rare. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Petrolatum

vaseline, soft paraffin

Formulation

Packaging:

- Petrolatum should be packed in a container that allows mixing of the petrolatum.
- When inhomogeneous, petrolatum should be mixed until homogeneous before dispensing from stock.

Storage:

- Petrolatum does not require special storage conditions.
- At temperatures higher than 30 °C bleeding or partial melting may cause inhomogeneity. Inhomogeneity does not affect the preparation, but requires proper mixing before dispensing or use.
- Petrolatum should preferably be used within 2 years.
- There are no major risks involved in the use of expired petrolatum.

Therapy:

- For external use only.
- Petrolatum has good protective properties and a strong occlusive effect. It is used as a protective and as a moisturising preparation. It is particularly useful for the management of dry skin in leprosy patients. Petrolatum is very difficult to remove from the skin. It is therefore unsuitable for hairy parts of the skin.
- Petrolatum is used as a vehicle for certain drugs, such as salicylic acid.

Dose:

- Apply petrolatum regularly to the skin.

Instructions for use:

- When used as a protective, apply petrolatum in a layer just thick enough to provide adequate protection.
- When used as a moisturizer, hydrate the skin first by keeping it wet for 10 to 15 minutes. This is done by taking a bath. Dry the skin surface and apply petrolatum in a thin layer.
- To remove petrolatum from the skin, rinse with some vegetable oil.
- Use petrolatum within 3 months after first opening the packaging.

Precautions:

- Do not use petrolatum in hot and/or humid climates, unless hydration of the skin is especially required.

Pregnancy/breast feeding:

- Harmful effects from external use of petrolatum have not been reported.

Side effects:
- Gross hydration due to the occlusive effect of petrolatum can cause complications such as secondary infections.
- Sensitisation reactions have been described due to constituents of yellow petrolatum. In contrast, sensitisation due to white petrolatum is rare. Inferior qualities of white petrolatum, however, may cause irritation of the skin. If sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Additional information:
- For the management of dry skin, especially for leprosy patients, local vegetable oils or emulsifying ointment are used instead of petrolatum.

Potassium permanganate stock solution
stock solution for dilution

Contains: 1% potassium permanganate in water.

Formulation

potassium permanganate	1	g
water	100	ml

Preparation:
1. Boil 120 ml water for 1 minute and allow to cool. Use this water for the preparation.
2. Dissolve the potassium permanganate in 100 ml of this water.
3. Make sure the dissolution is complete as undissolved crystals may be dangerous. This is done by carefully pouring the solution into a second flask and checking for undissolved crystals on the bottom of the first flask. Filtering is an alternative, however, this should not be done over a filter made from organic or metallic materials. Glass filters are suitable.

Packaging:
- The solution should be packed in a dark coloured, well closed glass bottle.
- Bottles should bear the warning: "Do not use undiluted".
- The amount required per patient depends on the instructions for use.
- Relatively small amounts are needed, because the stock solution has to be diluted immediately before use.

Storage:
- The stock solution should preferably be stored in a cool and dark place.
- The stock solution should be used within 1 month.
- Stock solutions containing degraded potassium permanganate are coloured brown instead of dark purple. In diluted solution degradation is easily observed, because they are brownish, not pink.
- Degraded solutions are less effective or even ineffective, and more staining may occur.

Therapy:
- For external use only. Should be diluted before use.
- Potassium permanganate solution has a strong antiseptic action and astringent properties, but it is rapidly inactivated after application. It is applied to the skin or used in the bath water. For the treatment of minor skin infections in leprosy, twice daily soakings with diluted potassium permanganate solution during 10-15 minutes are used.

Dose:
- Apply once or twice daily, dilute before use.

Instructions for use:
- The solution should be freshly diluted before each use. The stock solution should be diluted immediately before use with boiled and cooled water until a pink colour is obtained. The right colour has been described as "blotting paper pink" or "as pink as a fingernail." Approximately the right dilution is obtained by adding a teaspoon full of stock solution to about 300 ml water. In many countries this amount matches the contents of a Coca Cola bottle. Through its pink colour, potassium permanganate solution resembles soft drinks but is toxic. Therefore, the diluted solution should not be mixed or kept in a Coca Cola bottle.
- Wash the skin with water and soap and dry. During 10 minutes, wet the skin frequently with the diluted solution. Potassium permanganate solution is rapidly inactivated, so it should be reapplied often during the treatment period. Afterwards, rinse the skin thoroughly with water and dry. Discard the remainder of the diluted solution.
- Potassium permanganate is used for antiseptic baths in the same diluted concentration.
- Stains are removed from skin and bedding or textiles with a diluted sodium thiosulphate solution.
- Do not use the solution if it has a brown colour.

Precautions:
- Potassium permanganate crystals and strong solutions are very irritating and can cause severe chemical burns. Potassium permanganate dissolves very slowly in water. Therefore, crystals should never be dispensed to patients. In some countries tablets for dissolution are commercially available. Such tablets should not be given to patients as they may take them orally.
- Dilute the stock solution immediately before use.
- Potassium permanganate tablets and strong solutions are used vaginally in some regions for their supposed abortive effects. This application results in serious damage to the vaginal wall, corrosive burns, and peritonitis. Vascular collapse may result.
- Stains on the skin may occasionally be permanent, especially when the solution is used for prolonged periods of time.

Pregnancy/breast feeding:
– Harmful effects from external use of potassium permanganate solutions have not been reported.

Side effects:
– Potassium permanganate solutions stain the skin and all textiles contacting it. Skin staining may be permanent after prolonged use of the solution.

Intoxication:
– Potassium permanganate stock solution is irritating. Strong solutions and crystals are irritating and may cause severe chemical burns. After contact with skin or eyes rinse immediately with a lot of water.
– Ingestion causes nausea and vomiting. Liver and kidneys may get damaged, as well as the cardiovascular system. The fatal dose is assumed to be approximately 10 g for adults. Death may occur within a month after intoxication. After accidental ingestion give milk immediately to reduce absorption. Request for medical advice. Otherwise treatment is supportive and consists of keeping the patient warm, assisting respiration, etc.

Additional information:
– Some authors recommend dispensing potassium permanganate crystals to be dissolved at home. This is inadmissible. Potassium permanganate dissolves very slowly and ulcerations and chemical burns may result from very small undissolved crystals. For the same reason, tablets are unsuitable for dispensing to patients.
– The solution is rapidly inactivated by organic matter. Degradation of potassium permanganate is increased by its own degradation products. When the stock solution is filtered over organic or metallic filters, for example over paper filters or cotton wool, it will contain degradation products. As a result of this, it will not be stable and degrade fast.
– The solution is rapidly inactivated by the human skin. Therefore, it should be reapplied frequently during 10 minutes.

Povidone iodine solution 10%

Contains: povidone iodine 10% (active iodine 1%)

Formulation

povidone iodine		11	g
sodium dihydrogen phosphate anh		1.36	g
citric acid monohydrate		0.88	g
water	to	100	ml

Preparation:

1. Boil sufficient water for 1 minute and allow to cool. Use this water for the preparation.
2. Dissolve the sodium dihydrogen phosphate and the citric acid in approximately 70 ml water.
3. This mixture has a pH value of approximately 5. Adjust if necessary.
4. Slowly add the povidone iodine while stirring.
5. Continue stirring until homogeneous, heat should not be used.
6. Make up to volume with water.

Packaging:

– Povidone iodine solution should be packed in airtight containers which prevent evaporation of water and protect the solution from light.

Storage:

– Povidone iodine solution should be kept below 35 °C. The solution should be protected from light.
– Povidone iodine solution should be used within 3 months.
– During storage, evaporation of water or iodine, and degradation of iodine may occur. This will likely result in a solution with a lower active iodine concentration.
– Expired povidone iodine solutions may be less effective.

Therapy:

– For external use only.
– Povidone iodine releases iodine. Iodine has a strong antiseptic activity against all micro-organisms, including bacterial spores and viruses. It is used for disinfection of the skin and for wounds.

Dose:

– Disinfection of intact skin: apply the solution to the skin several minutes before the operation.
– Disinfection of wounds: apply the solution to the wound once or twice daily.

Instructions for use:

– Disinfection of intact skin: wash the skin carefully and apply the solution to the skin several minutes before the operation.
– Disinfection of wounds: clean the wound carefully. Iodine is inactivated by wound debris, blood and pus. After thorough cleaning apply the solution with a sterile dressing. Iodine treated skin should not be covered with a tight bandage.
– Do not use past the expiry date.

Precautions:

– Minor wounds healing satisfactory do not need disinfection.
– Iodine treated skin should not be covered with tight or occlusive bandages, because this causes irritation and blistering of the skin.
– Povidone iodine solution is very irritating to the eyes. After accidental contact, rinse the eyes immediately with a lot of water.

– Iodine is absorbed to some extent, even through intact skin. After absorption, it interferes with the thyroid function. Povidone iodine solution should therefore only be used with great care in patients with disorders of the thyroid gland (goitre etc.).

Pregnancy/breast feeding:
– Iodine is absorbed to some extent, even through healthy, intact skin. It passes the placenta and interferes with the thyroid function of the unborn child. Iodine preparations should therefore be avoided during pregnancy, unless there is a pressing necessity. Consider chlorhexidine as an alternative.
– Iodine is excreted in breast milk. It may interfere with the thyroid function of the newborn child. Iodine should therefore be avoided during breast feeding. Consider chlorhexidine as an alternative.

Side effects:
– Iodine is an irritating and sensitising substance. In the form of povidone iodine, it is usually better tolerated than the iodine used in the solution or tincture.
– Iodine and iodides may cause acne-like skin eruptions, bullous eruptions and tumour-like lesions.
– Iodine is absorbed to some extent, even through healthy, intact skin. After chronic use on large parts of the body, this may result in a characteristic pattern of systemic side effects called iodism. Iodism is characterized by mental depression, nervousness, insomnia, sexual impotence and thyroid disfunctioning. Children are more vulnerable to developing iodism than adults.

Intoxication:
– Iodine is corrosive and toxic when ingested. After accidental ingestion request for medical advice. While waiting for a doctor, give milk and starch first and then induce vomiting with syrup of ipecacuanha. When starch is unavailable, sodium thiosulphate solution can be used instead.

Additional information:
– Povidone iodine solution is often preferred to iodine as it is better tolerated. Povidone iodine releases iodine as the active substance and is therefore in most aspects comparable to iodine.
– Intact skin disinfection and wound care each need a different approach. In the first case, a rapid action is needed and irritation is not a problem. But in the second case, irritation and a delay in wound healing are important, while rapid action is less so because the contact time is much longer. For intact skin disinfection iodine tincture is often preferred. This is an irritating preparation, but it is very effective and has a rapid action. For wound care, the slower acting, but better tolerated, povidone iodine solution is preferred.

Salicyclic acid ointment 5%

Contains: 5% salicylic acid in petrolatum

Formulation

salicylic acid	5	g
petrolatum	95	g

Preparation:

1. Grind the salicylic acid. When sieves are available, sieve the salicylic acid, preferably through a 90 µm sieve.
2. Triturate the salicylic acid with an equal amount of petrolatum.
3. Add the rest of the petrolatum gradually and mix until homogeneous.

Packaging:

- Salicylic acid ointment should be packed in a container, which allows stirring of the ointment.
- Salicylic acid ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
- When inhomogeneous, salicylic acid ointment should be mixed until homogeneous before dispensing from stock.

Storage:

- Salicylic acid ointment should preferably be stored below 25 °C.
- The ointment should preferably be used within 2 years.
- Expired ointment may be less effective and more irritating. Salicylic acid ointment may get inhomogeneous at temperatures higher than 30 °C.
- Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:

- For external use only.
- Salicylic acid ointment has keratolytic and hydrating properties. It is used for the treatment of hyperkeratotic conditions and for psoriasis. Acne is best treated with a drying preparation, such as salicylic acid solution. This ointment should not be used for acne.
- Salicylic acid ointment is not easily washed away from the skin and is unsuitable for hairy parts of the skin.

Dose:

- Apply the ointment once or twice daily.

Instructions for use:

- Wash the skin before applying the ointment.
- Apply the ointment in a thin layer to prevent excessive hydration of the skin.
- The ointment is difficult to remove from the skin. It is helpful to first rinse the skin with vegetable oil.

– Do not use past the expiry date. Limit the use of salicylic acid ointment to the period the doctor has prescribed.

Precautions:
– Salicylic acid ointment should not be used for longer periods on large parts of the body, as this may lead to systemic intoxication.
– Small children should not receive salicylic acid ointment for long periods.

Pregnancy/breast feeding:
– Teratogenic effects of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans from external use of salicylic acid have not been described. Evaluate the benefit/risk ratio before using salicylic acid during pregnancy.
– Following external use salicylic acid is absorbed and excreted in breast milk. No adverse effects in the child have been reported following the mother's external use of salicylic acid. Evaluate the benefit/risk ratio before using salicylic acid during breast feeding.

Side effects:
– Sensitisation reactions due to constituents of yellow petrolatum have been described. Sensitisation due to white petrolatum is rare. Sensitisation to salicylic acid may develop in rare cases following long-term treatment.
– Inferior qualities of white petrolatum may cause irritation. Salicylic acid itself may also cause irritation. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.
– Salicylic acid inhibits blood coagulation. This effect is unlikely to raise clinical issues following external use of salicylic acid. However, people using anti-coagulants should only use salicylic acid containing preparations under close medical supervision.

Intoxication:
– Excessive or long-term use of salicylic acid containing preparations may cause systemic intoxication. This is unlikely to occur from using salicylic acid containing preparations on the skin, with the exception of long-term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Systemic intoxication is characterised by:
  • slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
  • more severe intoxication: excitation, confusion, fever and convulsions.
  • severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.

  When such effects occur, stop using the preparation immediately.

Additional information:
– Other concentrations of salicylic acid ranging from 2 to 6% can be used.

Salicyclic acid strong ointment 30%

Contains: 30% salicylic acid in petrolatum

Formulation

salicylic acid	30	g
petrolatum	70	g

Preparation:

1. Grind the salicylic acid. When sieves are available, sieve the salicylic acid, preferably through a 90 µm sieve.
2. Triturate the salicylic acid with an equal amount of petrolatum.
3. Add the rest of the petrolatum gradually and mix until homogeneous.

Packaging:

- Salicylic acid ointment should be packed in a container, which allows stirring of the ointment.
- Salicylic acid ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
- When inhomogeneous, salicylic acid ointment should be mixed until homogeneous before dispensing from stock.

Storage:

- Salicylic acid ointment should preferably be stored below 25 °C.
- The ointment should preferably be used within 2 years.
- Expired ointment may be less effective and more irritating.
- Salicylic acid ointment may get inhomogeneous at temperatures higher than 30 °C. Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:

- For external use only.
- Salicylic acid ointment has keratolytic and hydrating properties. Salicylic acid 30% ointment is used for the treatment of hyperkeratotic conditions such as corns and calluses and for common warts. Acne is treated with a drying preparation with a lower concentration, such as salicylic acid 5% solution. Salicylic acid strong ointment should not be used for acne or psoriasis.
- Salicylic acid ointment is not easily washed away from the skin and is unsuitable for hairy parts of the skin.

Dose:

- Apply the ointment once or twice daily.

Instructions for use:

- Wash the skin before application of the ointment.
- Apply the ointment in a thin layer to prevent excessive hydration of the skin.
- The ointment is difficult to remove from the skin. It is useful to first rinse the skin with vegetable oil.

– Do not use past the expiry date. Limit the use of salicylic acid ointment to the period the doctor has prescribed.

Precautions:
– Salicylic acid ointment should not be used for longer periods on large parts of the body, as this may lead to systemic intoxication.
– Small children should not receive salicylic acid ointment for long periods.
– Strong salicylic acid ointment (30%) is used for corns and calluses and salicylic acid ointment (5%) is used for psoriasis and various other hyperkeratotic skin conditions. Make sure not to confuse or confound the two.

Pregnancy/breast feeding:
– Teratogenic effects of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans from external use of salicylic acid have not been described. Evaluate the benefit/risk ratio before using salicylic acid during pregnancy.
– Following external use salicylic acid is absorbed and excreted in breast milk. No adverse effects in the child have been reported following the mother's external use of salicylic acid. Evaluate the benefit/risk ratio before using salicylic acid during breast feeding.

Side effects:
– Sensitisation reactions due to constituents of yellow petrolatum have been described. Sensitisation due to white petrolatum is rare. Sensitisation to salicylic acid may develop in rare cases after long-term treatment.
– Inferior qualities of white petrolatum may cause irritation. Salicylic acid itself may also cause irritation. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.
– Salicylic acid inhibits blood coagulation. This effect is unlikely to raise clinical issues following external use of salicylic acid. However, people using anti-coagulants should only use salicylic acid containing preparations under close medical supervision.

Intoxication:
– Excessive or long-term use of salicylic acid containing preparations may cause systemic intoxication. This is unlikely to occur from using salicylic acid containing preparations on the skin, with the exception of long-term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Systemic intoxication is characterised by:
  • slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
  • more severe intoxication: excitation, confusion, fever and convulsions.
  • severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.

  When such effects occur, stop using the preparation immediately.

Additional information:

– Other concentrations of salicylic acid ranging from 10% to 40% are used for corns and calluses. Concentrations between 2% to 6% are used for various hyperkeratotic skin conditions such as psoriasis.

Salicyclic acid solution 5%

Contains: 5% salicylic acid in an alcoholic solution.

Formulation

salicylic acid	5	g
industrial methylated spirit 70%	100	ml

Preparation:

1. Dissolve the salicylic acid in the industrial methylated spirit.

Packaging:

– Salicylic acid solution should be packed in a well closed container.

Storage:

– Salicylic acid solution should preferably be stored in a cool place.
– Salicylic acid solution is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where salicylic acid solution is stored.
– Salicylic acid solution should preferably be used within 3 months.
– Expired salicylic acid solution may have a lower alcohol content due to evaporation of alcohol. This will result in a higher salicylic acid content. When much alcohol has evaporated, the solution should be discarded.

Therapy:

– For external use only.
– Salicylic acid solution is used for the treatment of acne. It has keratolytic and drying properties. It is preferred over sulphur lotion, which can also be used in acne.

Dose:

– Apply the solution twice daily. Therapy generally needs to be continued for several months.

Instructions for use:

– Wash the skin with water and soap and dry. Apply the solution with some cotton wool or a clean piece of cloth, allow to dry.
– Do not use past the expiry date. Use salicylic acid solution within 1 month after dispensing.
– Close the bottle well after each use.

Precautions:

– Salicylic acid solution should not be used for extended periods of time on large parts of the body, as this may lead to systemic intoxication. Its use on small parts of the body for the treatment of acne is considered safe.
– Small children should not receive salicylic acid solution for long periods.

Pregnancy/breast feeding:
- Teratogenic effects of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans from external use of salicylic acid have not been described. Evaluate the benefit/risk ratio before using salicylic acid during pregnancy.
- Following external use salicylic acid is excreted in breast milk. No adverse effects in the child have been reported following the mother's external use of salicylic acid. Evaluate the benefit/risk ratio before using salicylic acid during breast feeding.

Side effects:
- Local irritation may occur, but is rare. When irritation or sensitisation reactions develop, stop using this preparation and do not use it again.
- Salicylic acid inhibits blood coagulation. This effect is unlikely to raise clinical issues following external use of salicylic acid. However, people using anti-coagulants should only use salicylic acid containing preparations under close medical supervision.

Intoxication:
- Excessive or long-term use of salicylic acid containing preparations may cause systemic intoxication. This is unlikely to occur following topical application of salicylic acid, unless for long-term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Systemic intoxication is characterised by:
  - slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
  - more severe intoxication: excitation, confusion, fever and convulsions.
  - severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.

  When such effects occur, stop using the preparation immediately.
- Accidental ingestion of salicylic acid solution produces complex clinical symptoms, because at least three toxic substances are involved: salicylic acid, alcohol and methanol. After accidental ingestion request for medical advice. While waiting for a doctor induce vomiting with syrup of ipecacuanha, and bring a 5% sodium bicarbonate solution in the stomach.

Additional information:
- Lower concentrations of salicylic acid, for example 2%, may be used.

Silver nitrate solution 0.5%

Contains: 0.5% silver nitrate in water.

Formulation

silver nitrate	0.5	g
water	100	ml

Preparation:

1. Boil 120 ml water for 1 minute and allow to cool. Use this water for the preparation.
2. Avoid contact of the silver nitrate with metallic or organic materials. Use glass or earthenware.
3. Dissolve the silver nitrate in 100 ml water.

Packaging:

– Silver nitrate solution should be packed in a well closed, dark coloured glass bottle. This bottle should not have a metallic cap. Metallic containers should not be used.

Storage:

– The solution should preferably be stored in a cool and dark place.
– The solution should be used within 1 week.
– Degraded solutions show a dark discolouration. Such solutions are less active and may be contaminated with micro-organisms causing infections. Degraded solutions should not be used.

Therapy:

– For external use only.
– Silver nitrate solution has strong antiseptic properties, and has some astringent effects. Silver nitrate solution is used for infection prevention in large deep burns. In primary health care, this solution is preferred over silver sulfadiazine cream for reasons concerning stability. Silver nitrate solution may also be used for the treatment of leg ulcers.

Instructions for use:

– Burns: silver nitrate treatment should be started immediately after burning, or at least within a few hours. After cleaning the wound and removal of necrotic and loose tissue the wound should be covered with several layers of sterile, course mesh gauze. These dressings are secured with circular bandages. The dressings have to be saturated with silver nitrate solution every two hours. Cover the dressings with light cotton to prevent excessive evaporation. The dressings should be kept saturated at all times. Dressings should be changed once daily.
– Ulcers: leg ulcers infected with *Pseudomonas* species are treated with silver nitrate compresses. The dressings should be changed every hour.
– Do not use past the expiry date.

Precautions:
- Silver nitrate solution prevents infection but is unable to sterilise the wound. Therefore, treatment should be started immediately after the burning, or at least within a few hours. Afterwards treatment rapidly becomes less effective, as the wound most likely has been contaminated with micro-organisms.
- The solution changes the wound appearance and delays rejection of necrotic tissue. As a consequence, careful wound management is required.
- Silver nitrate solutions of 1% or more may cause skin necrosis.
- The use of silver nitrate solution on large burns may cause hypochloremia.
- The use of silver nitrate solution on burns infected with nitrate-reducing micro-organisms may cause methaemoglobinaemia.

Pregnancy/breast feeding:
- Harmful effects from external use of silver nitrate solutions have not been reported.

Side effects:
- The solution causes staining of wounds and skin. Staining may be permanent. Silver nitrate solutions also stain clothes and bedding.
- Long-term use of silver nitrate solution may cause argyria, which is a slate-blue, irreversible discolouration of the skin.
- Silver nitrate solution may cause skin irritation.

Intoxication:
- Following accidental ingestion of silver nitrate solution request for medical advice. While waiting for a doctor administer 1% sodium chloride solution (table salt) in water several times. Empty the stomach using sodium sulphate as a purgative. When pain killers are required, paracetamol is preferred over aspirin.
- Upon contact with skin or eyes, immediately rinse with a lot of water. Sodium thiosulphate solution is used to treat chemical burns due to silver nitrate.

Additional information:
- Stains are removed with an aqueous solution containing 8% thiourea and 8% citric acid.
- When the water to prepare silver nitrate solution is rich in chlorides, a silver chloride precipitate will be formed. To avoid this reaction, use distilled water for the solution.
- Silver impregnated wound care materials are now commercially available. They are as expensive as silver nitrate solution, but are easier to handle and certainly much more stable.
- Since burn wound treatment requires specific expertise, patients should preferably be treated in specialised centres.

Silver sulfadiazine cream 1%

Contains: 1% silver sulfadiazine in a water washable cream.

Formulation

Commercial preparation. Silver sulfadiazine is commercially available under various trade names.

Packaging:

- See product specifications.
- The cream is sterile, and should not be repacked.

Storage:

- See product specifications.
- The cream should be stored at a temperature below 25 °C.
- After first opening the cream is readily contaminated with micro-organisms which may cause infections. Therefore, do not use the product longer than 7 days after first opening.
- Degraded creams show a slight greyish discolouration. They are less effective.
- The cream may get inhomogeneous at higher temperatures. Mixing the cream is not recommended as this is likely to result in microbial contamination. Exposure to temperatures higher than 25 °C should therefore be avoided.

Therapy:

- For external use only.
- Silver sulfadiazine cream is applied to deep extensive burns for infection prevention. In primary health care silver nitrate solution is preferred for stability reasons. Silver sulfadiazine cream can be used in specialised hospitals.

Dose:

- See product specifications.
- The cream should be applied to the wound at least once daily.

Instructions for use:

- See product specifications.
- Apply the cream to the wound in a layer of 2 - 3 millimetres. Apply directly on the wound or on a sterile gauze. A clean spatula is used to apply the cream.
- Do not use past the expiry date or when the cream has a pronounced grey colour. Do not use for more than 7 days after first opening the packaging.
- To wash away the cream, use a sterile isotonic sodium chloride solution.

Precautions:

- See product specifications.

- The cream prevents infection but is unable to sterilize the wound. Treatment should therefore be started immediately after burning, or at least within a few hours. Afterwards, treatment becomes rapidly less effective as the wound will already be infected with micro-organisms.
- The cream changes the wound appearance and delays rejection of necrotic tissue, and requires very careful wound management.

Pregnancy/breast feeding:
- Harmful effects from external use of silver sulfadiazine cream have not been reported, but systemic sulpha preparations are suspect. Whether maternal use of oral sulpha preparations during breast feeding presents a risk for the infant is still a matter of discussion, but the risk is low. The risk of externally used sulpha preparations is probably even lower. Evaluate the benefit/risk ratio before using this cream during pregnancy.

Side effects:
- See product specifications.
- Pain and a burning feeling may occur.

Additional information:
- The preparation of silver sulfadiazine cream should be done under special conditions to prevent contamination with micro-organisms. This is crucial because the cream is used on burn wounds and should be sterile. Therefore, we do not recommend preparation of silver sulfadiazine cream in a small scale facility under difficult conditions, and only the commercial preparation is included in this formulary.
- If, regardless the above mentioned arguments, the choice is made to produce silver sulfadiazine cream locally, a formulation for the cream can be found on www.openapo.info.

Sodium thiosulphate

Contains: sodium thiosulphate. After dissolution 10% sodium thiosulphate in water.

Formulation

sodium thiosulphate	30	g

Packaging:
- Sodium thiosulphate crystals should be packed in 30 g portions. Packaging materials should protect the crystals from humidity.
- Sodium thiosulphate crystals should be dissolved in water at home.
- One patient needs 30 g.

Storage:
- Sodium thiosulphate should preferably be stored in a cool and dry place.
- Sodium thiosulphate should preferably be used within 2 years.
- Expired sodium thiosulphate may be less effective.
- Ready for use sodium thiosulphate solution should preferably be used within 1 week.

Therapy:
- For external use only.
- Sodium thiosulphate is used for the treatment of pityriasis versicolor. This disease can also be treated with miconazole cream, which is much more expensive.

Dose:
- Apply the solution twice daily to the affected parts of the skin.

Instructions for use:
- Dissolve the crystals in approximately 300 ml clean water of potable quality. In many countries this is approximately the content of a Coca Cola bottle. The solution should preferably not be mixed or kept in a Coca Cola bottle, because it resembles soft drinks. When a Coca Cola or other soft drink bottle is used for the dissolution of sodium thiosulphate, mark this bottle clearly and keep it out of reach of children.
- Use the solution within 1 week and discard any leftovers.
- Wash the skin and dry. Scrub the solution to the affected parts of the skin with an old toothbrush or anything similar.
- In pityriasis versicolor, hypopigmented patches occur. These patches remain hypopigmented for some time, even after all the micro-organisms have been killed and the disease is fully treated. Repigmentation of the skin takes time. The presence of hypopigmented patches is therefore not an indication of treatment failure.

Precautions:
- Do not use the solution near the eyes.

Pregnancy/breast feeding:
- Harmful effects from external use of sodium thiosulphate solution have not been reported.

Side effects:
- Side effects are not expected.

Intoxication:
- Sodium thiosulphate is relatively non-toxic.

Additional information:
- Higher concentrations of sodium thiosulphate (up to 25%) are sometimes recommended. However, a 10% solution appears to be effective and is preferred.

- Sodium thiosulphate is used as an antidote in poisoning with iodine, cyanide, or bleaching powder, and for treatment of silver nitrate chemical burns.
- Sodium thiosulphate is dispensed as crystals for dissolution at home because the solution is unstable. As soon as sodium thiosulphate has been dissolved, it should preferably be used within 1 week. Old solutions may be contaminated with micro-organisms causing infections.

Strong Corticosteroid preparation

Formulation

Commercial preparations containing for example clobetasol dipropionate, betamethason valerate or betamethasone dipropionate in a cream or ointment (available under various trade names). These corticosteroids are considered class 3 or 4.

Packaging:

- See product specifications.

Storage:

- See product specifications.
- The preparation should preferably be stored in a cool and dark place. It should be stored below the maximum storage temperature mentioned in the product specifications.
- Expired corticosteroid preparations may be less effective.
- The preparation may get inhomogeneous at higher temperatures. When inhomogeneous, it should be mixed before dispensing or use.

Therapy:

- For external use only.
- These preparations contain very strong corticosteroids. They should only be used under medical supervision, for example in hospitals. Strong corticosteroids have very strong anti-inflammatory properties. They are used for various skin diseases, for example psoriasis.

Dose:

- See product specifications. Generally these preparations should be applied once or twice daily in a thin layer.
- General dosing recommendation for strong corticosteroids: during the first week apply the strong corticosteroid preparation in a thin layer twice daily. After this week switch to either hydrocortisone cream

or ointment, or apply the strong corticosteroid preparation twice a week and an indifferent vehicle twice daily during the remaining days. Emulsifying ointment, basic cream, and zinc oil are suitable indifferent vehicles.
– Do not use more than 30 g strong corticosteroid preparation per week.

Instructions for use:
– See product specifications.
– The preparation should be applied in a thin layer.
– Do not cover with wrappings or bandages unless on doctor's instructions.
– Do not use past the expiry date. Do not use for periods longer than 1 week unless on doctor's instructions.

Precautions:
– See product specifications.
– Do not use strong corticosteroid preparations on infections as they may worsen due to the corticosteroid.
– Apply strong corticosteroid preparations in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
– Corticosteroid preparations can only give symptomatic relief. When treatment is stopped, the disease may return.
– In children, growth retardation may result from prolonged use of corticosteroids on the skin. Regular checks on both length and weight is recommended for children during treatment with corticosteroids on the skin, especially when large quantities are used, or use during prolonged periods of time.
– Avoid contact of strong corticosteroid preparations with the eyes and the skin around the eyes.

Pregnancy/breast feeding:
– Corticosteroids in high systemic doses were teratogenic in animal experiments. Corticosteroids applied to the skin are absorbed to some extent, pass the placenta and may influence the unborn child. However, harmful effects from external use of strong corticosteroids have not been reported. Carefully evaluate the need for treatment during pregnancy.
– Corticosteroids are excreted in breast milk, but adverse effects in the baby resulting from the mother's external use of strong corticosteroids have not been reported. Carefully evaluate the need for treatment during breast feeding.
– See also the product specifications.

Side effects:
– See product specifications.
– Corticosteroid preparations mask infections.
– Corticosteroid preparations may delay healing of damaged skin.
– Local side effects of corticosteroid preparations include thinning of the skin, irritation, an itching or burning sensation, and depigmentation. These effects are most likely to occur in the face, on hairy parts of the body, and in the genital region.
– Systemic side effects may result from local use of strong corticosteroid preparations. They may be very serious, such as suppression of the corticosteroid synthesis in the adrenal glands.
– Sensitisation reactions are rare but have been described. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

- Strong corticosteroid preparations have a much stronger effect than hydrocortisone preparations. However, the skin gets used to treatment with strong corticosteroids, and in the long run even high doses have a reduced effect, in combination with a higher risk for developing serious side effects. This is called tachyphylaxis. Also, the treatment risks of strong corticosteroid preparations are much higher than with hydrocortisone. Strong corticosteroid preparations should only be used when hydrocortisone is found to be ineffective. When using a strong corticosteroid preparation, switch to hydrocortisone or to a twice weekly application of the strong corticosteroid, as soon as the skin disease has calmed down.
- It is common practice to dilute strong corticosteroid preparations, but this often results in unstable preparations. Therefore, we discourage this practice. When dilution is required, petrolatum is the best choice to obtain a reasonably stable preparation. Such a diluted preparation should be used within 1 week.
- Strong corticosteroids cannot be processed in the basic cream or emulsifying ointment formulations of this formulary, because it will produce unstable preparations. The preparation of strong corticosteroid preparations requires experienced personnel, especially because poorly mixed preparations may result in poor efficacy and a high risk of side effects. For these reasons we did not include such a formula. A formula is found on www.openapo.info.

Sulphur cream 10%

Contains: 10% sulphur in basic cream.

Formulation

sulphur	10	g
basic cream	90	g

Preparation:

1. If the sulphur contains large lumps, rub it gently between two clean sheets of paper.
2. Triturate the sulphur with approximately 10 g basic cream.
3. Add the rest of the cream gradually and mix until homogeneous.

Packaging:

- Sulphur cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The packaging should allow stirring of the cream.
- The cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.
- When inhomogeneous, sulphur cream should be mixed until homogeneous before dispensing from stock.

Storage:

- Sulphur cream should preferably be stored below 40 °C.

- The cream should preferably be used within 3 months.
- Expired creams risk being contaminated with micro-organisms causing infections.
- Sulphur cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
- If the container is not closed properly, water may evaporate during storage. This results in a preparation resembling sulphur ointment, with a sulphur content between 10 and 20%.

Therapy:

- For external use only.
- Sulphur cream is used to treat scabies. This cream is unsuitable for the treatment of acne, for which indication salicylic acid solution 5% is recommended.
- Lindane cream is used for the treatment of scabies and lice infestations. It is water washable, suitable for hairy parts of the skin, and is effective after a single application. Due to environmental concerns lindane is no longer available in many countries. Benzyl benzoate is the first alternative, but sulphur 10% can also be used. Sulphur cream is washable and suitable for hairy parts of the skin.
- For the treatment of pityriasis versicolor sodium thiosulphate solution is preferred because it is cheaper and has better drying qualities.

Dose:

- Apply the cream on seven consecutive evenings after washing the skin. An adult needs approximately 250 g for a complete treatment period.

Instructions for use:

- When inhomogeneous mix the cream before use.
- Wash the skin thoroughly and apply the cream to the whole body in the evening. Make sure the cream contacts the whole body, including skin folds. Wash away in the morning. Repeat this every evening during 1 week (total 7 days). Wash all clothes, bed sheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water, to prevent reinfestation. It is also recommended to shake out blankets and outer wear.
- Itch may persist for weeks after all the mites have been killed. Do not repeat treatment but use some calamine lotion to relieve the itch.
- After the treatment period, discard any remaining cream.

Precautions:

- Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.

Pregnancy/breast feeding:

- Harmful effects from external use of sulphur preparations have not been reported.

Side effects:

- Sensitisation due to methylparaben used as preservative in the cream may occur, but is rare in this concentration. Sensitisation due to yellow petrolatum may occur, but is rare.
- Irritation to lanette wax has been described. Inferior qualities of white petrolatum may also cause irritation.

– Sulphur itself may also cause skin irritation. If sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

– When larger quantities of sulphur cream are prepared for stock storage, a freshly prepared basic cream should be used.
– Sulphur can be used in lower concentrations in the same cream for other indications. It is unknown if lower concentrations are effective against scabies.
– When basic cream is unavailable, sulphur ointment can be used instead. For other alternative vehicles see the monograph on sulphur ointment.

Sulphur lotion 3%

sulphur/calamine lotion

Contains: 3% sulphur, 20% zinc oxide, 0.4% phenol in an aqueous vehicle.

Formulation

sulphur		3	g
zinc oxide		20	g
bentonite		3	g
trisodium citrate		0.5	g
glycerin		5	ml
liquefied phenol		0.5	ml
water	to	100	ml

Preparation:

1. Boil 100 ml water for 1 minute and allow to cool. Use this water for the preparation.
2. Dissolve the trisodium citrate in 70 ml water.
3. If the sulphur contains large lumps, rub it gently between two clean sheets of paper.
4. When sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
5. Mix the sulphur with the zinc oxide and with the bentonite.
6. Triturate this mixture with the glycerin and 20 ml citrate solution.
7. Add the rest of the citrate solution and mix until homogeneous.
8. Add the liquefied phenol and mix.
9. Add enough recently boiled and cooled water to produce 100 ml and mix well.

Packaging:
- Sulphur lotion should be packed in well closed containers, which prevent evaporation of water and contamination with micro-organisms, and protect the lotion from exposure to light.
- Sulphur lotion should be shaken until homogeneous before dispensing from stock.

Storage:
- Sulphur lotion should preferably be stored below 40 °C.
- Sulphur lotion should preferably be used within 3 months.
- Expired sulphur lotions may be less effective, and may be contaminated with micro-organisms causing infections.
- Sedimentation of solids may occur during storage. The lotion should always be shaken before dispensing or use.

Therapy:
- For external use only.
- Sulphur lotion has general soothing, cooling, antiseptic and antipruritic properties. It has a keratolytic effect which helps to prevent blackheads. It is used in acne, particularly in acne rosacea. However, the effect of sulphur on keratinisation is difficult to predict. Sulphur may also exert a parakeratotic effect which increases the number of blackheads and worsens the acne. Therefore, salicylic acid solution is preferred in acne. Sulphur cream and ointment are indicated for scabies and not for acne, because these preparations have a high concentration of sulphur and slightly occlusive and hydrating effects.

Dose:
- Apply the lotion twice daily. Therapy must generally be continued for several months.

Instructions for use:
- Shake the lotion before use.
- Wash the skin with water and soap and allow to dry. Apply the lotion with some cotton wool or with a clean piece of cloth. Allow to dry and leave exposed to the air. Do not cover the affected parts with bandages.
- Do not use past the expiry date. Use within 1 month after dispensing.

Precautions:
- Sulphur lotion should cautiously be used on wounds because of the risk of phenol absorption.
- Sulphur lotion should not be used on large parts of the body for a period longer than 1 week, unless on doctor's instructions. Systemic side effects may result from absorption of phenol.
- Avoid contact of sulphur lotion with the eyes.

Pregnancy/breast feeding:
- Harmful effects from external use of sulphur lotion have not been reported. However, evaluate the benefit/risk ratio before using this preparation during pregnancy or breast feeding

Side effects:
- The effect of sulphur on keratinisation is difficult to predict. Keratolytic effects result in a decrease in blackheads, but lower concentrations of sulphur may also exert a parakeratotic effect which increases the number of blackheads and worsens the acne.
- Sensitisation reactions with a burning feeling are rare but may occur. If so, stop using the lotion immediately.

Intoxication:
- When sulphur lotion is ingested accidentally request medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

Additional information:
- The formula is based on the modified calamine lotion in this formulary. More information is found in the monograph on calamine lotion.
- When sulphur lotion is prepared in small quantities for immediate dispensing, preparation is much easier than described above. The preparation then reads: triturate 3 g sulphur gradually with 98 g calamine lotion ready for use.
- Other concentrations of sulphur (up to 6%) can be used. In lower concentrations, e.g., 2%, sulphur has a parakeratotic effect which may worsen acne. Higher sulphur concentrations produce a more pronounced drying effect.

Sulphur ointment 10%

Contains: 10% sulphur in emulsifying ointment.

Formulation

sulphur	10	g
emulsifying ointment	90	g

Preparation:
1. If the sulphur contains large lumps, rub it gently between two clean sheets of paper.
2. Triturate the sulphur with approximately 10 g emulsifying ointment.
3. Add the rest of the ointment gradually and mix until homogeneous.

Packaging:
- Sulphur ointment should be packed in a container which allows stirring. The ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
- When inhomogeneous, sulphur ointment should be mixed until homogeneous before dispensing from stock.

Storage:
- The ointment should preferably be stored below 25 °C.
- The ointment should preferably be used within 2 years.
- Ointments older than 2 years may show a changed consistency and may be less effective.
- Sulphur ointment may get inhomogeneous at temperatures higher than 25 °C. Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:
- For external use only.
- Sulphur ointment is used for scabies. This ointment is not suitable for the treatment of acne, for which we recommend salicylic acid solution 5%.
- Lindane cream is used for the treatment of scabies and lice infestations. It is water washable, suitable for hairy parts of the skin, and is effective after a single application. Due to environmental concerns lindane is no longer available in many countries. Benzyl benzoate is the first alternative, but sulphur 10% can also be used. Sulphur ointment is washable and suitable for hairy parts of the skin.
- For pityriasis versicolor sodium thiosulphate solution is preferred because it is cheaper and has better drying qualities.

Dose:
- Apply the ointment on seven consecutive evenings after washing the skin. An adult needs approximately 400 g for a complete treatment period.

Instructions for use:
- When inhomogeneous mix the ointment before use.
- Wash the skin thoroughly and apply the ointment to the whole body in the evening. Make sure the ointment contacts the whole body, including skin folds. Wash away in the morning. Repeat this every evening during 1 week (total 7 days). Wash all clothes, bed sheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water, to prevent reinfestation. It is also recommended to shake out blankets and outer wear.
- Itch may persist for weeks after all the mites have been killed. Do not repeat treatment, but use some calamine lotion to relieve the itch.
- Discard any remaining ointment after treatment.

Precautions:
- Thick layers of sulphur ointment have occlusive and hydrating properties which may cause infections and exacerbation of the skin disease.

Pregnancy/breast feeding:
– Harmful effects from external use of sulphur preparations during pregnancy or breast feeding have not been reported.

Side effects:
– Sulphur ointment may cause an increase in blackheads and exacerbation of acne.
– Sensitisation due to yellow petrolatum may occur but is rare. When sensitisation occurs, stop using the ointment.
– Irritation to lanette wax has been described. Inferior qualities of white petrolatum may cause irritation too.
– Sulphur itself may cause some skin irritation. If sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:
– When larger quantities of sulphur ointment are prepared for storage, a freshly prepared emulsifying ointment should preferably be used.
– Sulphur can be used in lower concentrations in this ointment for other indications. It is unknown if lower concentrations are effective against scabies.
– When emulsifying ointment is unavailable, sulphur cream can be used instead. When this is also unavailable, sulphur can be incorporated in petrolatum. However, this is an occlusive preparation with a high sensitisation potential. Sulphur in petrolatum is very difficult to wash away.

Sunscreen FAA

Contains: titanium dioxide 10% and octinoxate 8% in petrolatum.

Formulation

titanium dioxide	10	g
octinoxate	8	g
petrolatum	82	g

Preparation:
1. Grind the titanium dioxide. When sieves are available, sieve the titanium dioxide, preferably through a 90 µm sieve.
2. Melt the petrolatum by heating it gently to approximately 60 °C until all petrolatum has melted.
3. Triturate the titanium dioxide carefully with approximately 10 g molten petrolatum and mix until homogeneous.

4. Add the rest of the petrolatum gradually and mix after each addition.
5. Add the octinoxate and mix until homogeneous.
6. Continue mixing until the mixture has cooled to room temperature.

Packaging:
- Sunscreen FAA should be packed in a well closed container, which prevents contamination with micro-organisms. The container should allow stirring of the cream. Sunscreen FAA should not be packed in collapsible tubes when the storage temperature may exceed 35 °C.
- When inhomogeneous, sunscreen FAA should be mixed until homogeneous before dispensing from stock.

Storage:
- Sunscreen FAA should preferably be stored below 30 °C.
- Sunscreen FAA should preferably be used within 2 years.
- Expired sunscreen may be less effective and more irritating.
- Sunscreen FAA may get inhomogeneous at temperatures higher than 35 °C. Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:
- For external use only.
- Sunscreen FAA is used for protection from UV sunlight for people with albinism or who are extremely sensitive to sunlight.
- Sunscreen FAA is difficult to wash away. If washing away is a problem, rinse first with some vegetable oil. Sunscreen FAA is unsuitable for hairy parts of the body.
- Proper sun protection involves more than a sunscreen, and includes wearing tightly knit, loose fitting clothes and a broad brimmed hat.

Dose:
- Sunscreen FAA should be applied several times a day before going outdoors.

Instructions for use:
- Apply sunscreen FAA several times a day before going outdoors. Apply in a normal layer and rub into the skin.
- Do not use past the expiry date. Sunscreen FAA may be required for longer periods of time.

Precautions:
- When applied in a thick layer, sunscreen FAA can be occlusive and cause infections.

Pregnancy/breast feeding:
- No harmful effects to the mother or unborn child are known, but the safety of this preparation in pregnancy has not been established.

Side effects:
- Sensitisation to sunlight (photosensitisation reactions) have been described but are uncommon.

– Sensitisation due to yellow petrolatum may occur but is rare. When sensitisation occurs stop using the sunscreen and do not use it again.

Additional information:

– This formula is based on the sunscreen of the Dutch Foundation African Albino's.
– When titanium dioxide is unavailable zinc oxide can be used instead. The usual concentration of zinc oxide in sunscreens is 20%. The formula then reads: zinc oxide 20 g, octinoxate 8 g, petrolatum 72 g.

Tar cream 3%

Contains: 3% coal tar in basic cream.

Formulation

coal tar	3	g
basic cream	97	g

Preparation:

1. Mix the coal tar carefully with approximately 20 g cream.
2. Add the rest of the cream gradually and mix until homogeneous.

Packaging:

– Tar cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The packaging should allow stirring of the cream. Tar cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.
– When inhomogeneous, tar cream should be mixed until homogeneous before dispensing from stock.

Storage:

– Tar cream should preferably be stored below 40 °C.
– The cream should preferably be used within 3 months.
– Expired creams risk being contaminated with micro-organisms causing infections.
– Tar cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
– If the container is not closed properly, water may evaporate during storage. This results in an emulsifying ointment type preparation with a tar content between 3 and 6%.

Therapy:

- For external use only.
- Tars are keratoplastic agents with weak antiseptic and antipruritic effects. They are used in psoriasis and eczema. Tar cream has only slightly moisturising effects.
- The preparation is washable and is suitable for hairy parts of the skin. Coal tar can also be incorporated in an alcoholic solution, which gives a more drying preparation, and in zinc paste, which produces a more protective preparation.

Dose:

- Apply twice daily to the affected parts of the skin.

Instructions for use:

- When inhomogeneous, mix the cream before use.
- Wash the skin carefully before application. Apply the cream in a thin layer to the affected parts of the skin. Rub it gently into the skin.
- Do not use past the expiry date. Do not use for more than 1 month unless on doctor's instructions. Use within 1 month after dispensing.

Precautions:

- Tar preparations stain the skin, clothes and bedding.
- Tars have a phototoxic effect. Exposure to sunlight should be avoided during tar therapy, at least until 24 hours after the last application.
- Avoid application to large skin surfaces and healthy parts of the skin.
- Apply tar cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.

Pregnancy/breast feeding:

- Harmful effects from external use of tar preparations during pregnancy or breast feeding have not been reported, but safety has not been proven either. Carefully evaluate the need for treatment during pregnancy or breast feeding. Other preparations used in psoriasis (dithranol, strong corticosteroids, oral etretinate) constitute higher risks during pregnancy. Pregnancy itself may have a beneficial effect on psoriasis.

Side effects:

- Tar preparations may cause skin irritation and folliculitis. Irritation may also be due to lanette wax or to inferior qualities of white petrolatum used in the cream.
- Coal tar has a low sensitisation potential. Sensitisation due to methylparaben may develop but is rare with the concentration used in this cream. Sensitisation due to yellow petrolatum may occur but is rare. If sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Additional information:

- Larger quantities of coal tar can be incorporated in this cream, but will affect the stability of the cream.
- When larger quantities of tar cream are prepared for storage, a freshly prepared basic cream should be used.

– When basic cream is unavailable, tar paste or tar solution can be used. Emulsifying ointment, petrolatum with 10% wool fat, or plain petrolatum, are less suitable vehicles because they are occlusive, but can be used when basic cream is unavailable.

Tar paste 5%

Contains: 5% coal tar in zinc paste.

Formulation

coal tar	5	g
zinc paste	95	g

Preparation:

1. Mix the coal tar carefully with approximately 10 g zinc paste. Gentle heat may be used.
2. Add the rest of the paste gradually and mix until homogeneous.

Packaging:

– The paste should be packed in a well closed container with a wide opening allowing easy dispensing from the container. Collapsible tubes are inappropriate as it may be difficult to remove the paste from them.

Storage:

– Tar paste should preferably be stored below 40 °C.
– Tar paste should preferably be used within 2 years.
– Expired pastes may be less effective and have altered consistency.

Therapy:

– For external use only.
– Tars are keratoplastic agents with weak antiseptic and antipruritic activity. They are useful for the treatment of psoriasis and eczema. Tar paste has a protective effect. Coal tar can also be incorporated in a cream which results in a more penetrating preparation, or in a solution for a more drying preparation.
– Tar paste is very difficult to wash away from the skin. Therefore it is unsuitable for hairy parts of the skin.

Dose:

– Apply the paste twice daily to the affected parts of the skin.

Instructions for use:
- Wash the skin carefully before application.
- Apply the paste in a layer just thick enough to provide adequate protection.
- A loose bandage may be used for more protection and to keep the paste in place.
- To remove the paste rinse with some vegetable oil first.
- Do not use past the expiry date. Do not use for periods longer than 1 month unless on doctor's instructions. Use within 1month after dispensing.

Precautions:
- Tar preparations stain the skin, clothes and bedding.
- Tars may have a phototoxic effect. Exposure to sunlight should be avoided during tar therapy, at least until 24 hours after the last application.
- Avoid application to large skin surfaces and healthy parts of the skin.

Pregnancy/breast feeding:
- Harmful effects from external use of tar preparations during pregnancy or breast feeding have not been reported, but safety has not been proven either. Carefully evaluate the need for treatment during pregnancy or breast feeding. Other preparations used in psoriasis (dithranol, strong corticosteroids, oral etretinate) constitute higher risks during pregnancy. Pregnancy itself may have a beneficial effect on psoriasis.

Side effects:
- Tar preparations may cause skin irritation and folliculitis. Irritation may also result from using inferior qualities of white petrolatum in the paste.
- Coal tar has a low sensitisation potential. Sensitisation due to yellow petrolatum may occur but is rare. When sensitisation or severe irritation reactions develop, stop using the preparation and do not use it again.

Additional information:
- Lower concentrations of tar are prepared by further diluting the paste.
- When larger quantities are prepared for stock storage, a freshly prepared zinc paste should preferably be used.
- When zinc paste is unavailable, tar solution or tar cream can be used instead. Emulsifying ointment, petrolatum with 10% wool fat, or plain petrolatum are less suitable vehicles because they are occlusive, but can be used when more appropriate vehicles are unavailable.

Tar solution 20%

Contains: 20% coal tar in an alcoholic solution.

Formulation

coal tar	20	g
polysorbate 80	5	g
industrial methylated spirit 95%	to 100	ml

Preparation:

1. Mix the coal tar with the polysorbate 80.
2. Pour this mixture into approximately 80 ml industrial methylated spirit 95%. Shake the mixture occasionally during one hour.
3. Allow to stand for 24 hours.
4. Decant and filter.
5. Add enough industrial methylated spirit to produce 100 ml and mix well.

Packaging:

– Tar solution should be packed in a well closed container.

Storage:

– Tar solution should be stored under cool conditions.
– Tar solution is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where tar solution is stored.
– Tar solution should preferably be used within 3 months.
– Expired tar solutions may have a higher tar content due to evaporation of alcohol. Such solutions should not be used.
– Evaporation of alcohol may occur if the packaging is not closed well. This results in a solution with a higher tar content.

Therapy:

– For external use only.
– Tars are keratoplastic agents with weak antiseptic and antipruritic effects. They are useful for the treatment of psoriasis and eczema. Tar solution has a drying effect.
– Tar solution is washable and consequently is suitable for hairy parts of the skin. Coal tar can be incorporated in a cream, which results in a more penetrating preparation, or in a paste for a more protective preparation.

Dose:

– Apply the solution to the affected parts of the skin twice daily.

Instructions for use:
- Wash the skin carefully. Apply the solution to the skin. Do not cover with a bandage.
- Do not use past the expiry date. Do not use for periods longer than 1 month unless on doctor's instructions. Use within 2 weeks after dispensing.
- Close the bottle well after use.

Precautions:
- Tar preparations stain the skin, clothes and bedding.
- Tar solution is highly flammable.
- Tars may have a phototoxic effect. Exposure to sunlight should be avoided during tar therapy, at least until 24 hours after the last application.
- Avoid application to large skin surfaces and healthy parts of the skin.

Pregnancy/breast feeding:
- Harmful effects from external use of tar preparations during pregnancy or breast feeding have not been reported, but safety has not been proven either. Carefully evaluate the need for treatment during pregnancy or breast feeding. Other preparations used in psoriasis (dithranol, strong corticosteroids, oral etretinate) constitute higher risks during pregnancy. Pregnancy itself may have a beneficial effect on psoriasis.

Side effects:
- Tar preparations may cause skin irritation and folliculitis. Irritation may also be due to the alcohol.
- Coal tar has a low sensitisation potential. If sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Intoxication:
- After accidental ingestion request medical advice. The clinical symptoms after ingestion are complex, as intoxication is due to tar, ethanol and methanol. While waiting for a doctor induce vomiting with syrup of ipecacuanha and bring a 5% sodium bicarbonate solution in the stomach.

Additional information:
- This formula is equivalent to the one in the *British Pharmacopoeia*. Various other, slightly different formulations are given in other pharmacopoeias.
- Lower concentrations of tar may be used.
- The solution contains only the soluble tar ingredients that were extracted. Therefore, it may be less effective than other tar preparations such as creams. The relative efficacy also depends on the exact composition of the tar.
- When tar solution is unavailable, tar cream or tar paste can be used instead. Emulsifying ointment, petrolatum with 10% wool fat, or plain petrolatum are less suitable vehicles because they are occlusive, but can be used when more appropriate vehicles are unavailable.

Urea cream 10%

Contains: 10% urea in basic cream

Formulation

urea	10	g
basic cream	90	g

Preparation:

1. Triturate the urea carefully with 30 g basic cream and mix until homogeneous.
2. Add the rest of the cream gradually and mix until homogeneous.

Packaging:

- Urea cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The packaging should allow stirring of the cream. Urea cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.
- When inhomogeneous, urea cream should be mixed until homogeneous before dispensing from stock.

Storage:

- The cream should be stored in a cool place.
- The cream should preferably be used within 1 month.
- Expired creams may be less effective due to degradation of urea. The odour of ammonia indicates degradation.
- Expired creams also risk being contaminated with micro-organisms causing infections.
- Urea cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
- If the container is not closed properly, water may evaporate during storage. This results in a cream with less water, and a higher urea content. Such creams are more effective but also produce more side effects. Eventually, evaporation of water can result in a useless mixture of fatty constituents and crystalline urea that should be discarded.

Therapy:

- For external use only.
- Urea cream has strong moisturising properties. It is used to hydrate the skin, for example in ichthyosis. Urea cream is easily washed away from the skin.
- For simple dry skin problems a less powerful and cheaper emollient is preferred, such as emulsifying ointment or even petrolatum. Urea cream is somewhat less effective but better tolerated than urea ointment.

Dose:

- Apply in a thin layer twice daily.

Instructions for use:
- Wash the skin carefully with water and soap. Hydrate the skin by keeping it wet for 10 to 15 minutes, for example by taking a bath. When the cream is inhomogeneous, mix it before use. Apply the cream in a thin layer.
- It may take several days before results are seen.
- Do not use past the expiry date

Precautions:
- Do not apply urea cream near the eyes.

Pregnancy/breast feeding:
- Harmful effects from external use of urea cream have not been reported.

Side effects:
- Urea cream may produce a burning feeling, particularly when used in the face or on broken skin. This is no reason to stop treatment.
- Sensitisation due to methylparaben may occur, but is rare with the concentration used in this cream. Sensitisation due to yellow petrolatum may occur, but is rare.
- Irritation due to lanette wax has been described. Inferior qualities of white petrolatum may also cause irritation. If sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:
- This formula is analogous to the one in the *Formulary of Dutch Pharmacists*. It is based on the formulation of basic cream. More information on the formulation and alternative starting materials is found in the monograph on basic cream.

Urea ointment 10%

Contains: 10% urea in emulsifying ointment

Formulation

urea	10	g
water	20	g
emulsifying ointment	70	g

Preparation:

1. Boil 40 ml water for 1 minute and allow to cool. Use this water for the preparation.
2. Dissolve the urea in 20 ml of this water.
3. Mix the urea solution carefully with the emulsifying ointment, by small quantities at a time, until homogeneous.

Packaging:

- Urea ointment should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The packaging should allow stirring of the ointment. Urea ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
- When inhomogeneous, urea ointment should be mixed until homogeneous before dispensing from stock.

Storage:

- The ointment should preferably be stored in a cool place.
- The ointment should preferably be used within 1 month.
- Urea ointment may get inhomogeneous at temperatures higher than 25 °C. Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.
- Expired ointments may be less effective due to degradation of urea. The odour of ammonia indicates degradation.
- Expired ointments also risk being contaminated with micro-organisms causing infections.
- If the container is not closed properly, water may evaporate during storage. This results in a useless mixture of fatty constituents and crystalline urea that should be discarded.

Therapy:

- For external use only.
- Urea ointment has strong moisturising properties. It is used to hydrate the skin, for example in ichthyosis. Urea ointment is easily washed away from the skin.
- For simple dry skin problems a less powerful and cheaper emollient is preferred, such as emulsifying ointment or even petrolatum.
- Urea ointment is somewhat more effective, but less well tolerated than urea cream.

Dose:

- Apply in a thin layer twice daily.

Instructions for use:

- Wash the skin carefully with water and soap. Hydrate the skin by keeping it wet for 10 to 15 minutes, for example by taking a bath. If inhomogeneous, mix the ointment before use. Apply the ointment in a thin layer.
- It may take several days before results are seen.
- Do not use past the expiry date.

Precautions:

- Do not apply urea ointment near the eyes.

Pregnancy/breast feeding:
– Harmful effects from external use of urea ointment have not been reported.

Side effects:
– Urea ointment may produce a burning feeling, particularly when used in the face or on broken skin. This is no reason to stop treatment.
– Sensitisation due to yellow petrolatum may occur, but is rare.
– Irritation due to lanette wax has been described. Inferior qualities of white petrolatum may also cause irritation. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:
– This formula is analogous to the one in the *Formulary of Dutch Pharmacists*. It is based on the formulation of emulsifying ointment. More information on the formulation and alternative starting materials is found in the monograph on emulsifying ointment.
– The water is used for easier processing of urea and to ensure homogeneous distribution in the ointment. Direct trituration of urea with emulsifying ointment is possible, but often results in an inhomogeneous preparation containing urea crystals.

Water

Formulation
water

Preparation:
1. The water should be at least of potable quality. Boil the water for 1 minute and allow to cool. Cover the container loosely during cooling.

Packaging:
– Water should be kept in a clean and well closed container.

Storage:
– Water should always be freshly boiled and cooled.
– When allowing water to cool, the container should be covered loosely, to prevent micro-organisms or dust particles to fall in. Covering should preferably be done with a glass watch.

– Water that has been stored, even for a limited time, may be contaminated with micro-organisms. They may cause infections when the water is applied to the skin.

Therapy:

– Water has general cooling properties. It is used in various skin diseases by application with compresses.

Whitfield's cream 5%-5%

benzoic and salicylic acid cream.

Contains: benzoic acid 5% and salicylic acid 5% in basic cream.

Formulation

benzoic acid	5	g
salicylic acid	5	g
basic cream	90	g

Preparation:

1. Grind the benzoic acid and the salicylic acid. When sieves are available, sieve the benzoic acid and the salicylic acid, preferably through a 90 µm sieve.
2. Mix the benzoic acid with the salicylic acid.
3. Triturate this mixture with approximately 10 g basic cream.
4. Add the rest of the cream gradually and mix until homogeneous.

Packaging:

– The cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The container should allow stirring of the cream. Whitfield's cream should not be packed in collapsible tubes when the storage temperature may exceed 40 °C.
– When inhomogeneous, Whitfield's cream should be mixed until homogeneous before dispensing from stock.

Storage:

– Whitfield's cream should preferably be stored below 40 °C.
– The cream should preferably be used within 3 months.
– Expired creams may be less effective and risk being contaminated with micro-organisms causing infections.

- Whitfield's cream may get inhomogeneous at temperatures higher than 40 °C. Inhomogeneity does not affect the cream, but requires proper mixing before dispensing or use.
- If the container is not closed properly, water may evaporate during storage. This results in a preparation like Whitfield's ointment with higher contents of benzoic acid and salicylic acid. Such preparations are more sensitising and irritating.

Therapy:

- For external use only.
- Whitfield's cream combines a fungistatic activity with keratolytic properties. It is used for superficial skin infections caused by fungi, such as ringworm and athlete's foot. *Candida* species are insensitive.
- The cream is less hydrating than the ointment and is preferred in most cases. Non responsive cases may be treated with miconazole cream.

Dose:

- The cream should be applied twice daily in a thin layer to the affected parts of the skin. Treatment may take several weeks.

Instructions for use:

- Wash the skin with water and soap. Apply the cream in a thin layer and rub it into the skin. Whitfield's cream should only be applied to affected parts of the skin.
- Do not use past the expiry date. Use within 1 month after dispensing.

Precautions:

- In small children, do not use the cream on large parts of the body or for prolonged periods of time.
- Apply Whitfield's cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Do not use the cream for a patient who is known to be allergic to one of the constituents. If sensitisation reactions develop, stop using the cream immediately.
- Ringworm and athlete's foot are highly contagious. If possible, close contacts (family, school) should be examined and treated if necessary.
- Good personal hygiene and careful drying of the skin are essential to prevent reinfection.

Pregnancy/breast feeding:

- Teratogenic effects of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans from external use of salicylic acid have not been described. Evaluate the benefit/risk ratio before using salicylic acid during pregnancy.
- Following external use salicylic acid is excreted in breast milk. No adverse effects in the child have been reported following the mother's external use of salicylic acid. Evaluate the benefit/risk ratio before using salicylic acid during breast feeding.

Side effects:

- Sensitisation may occur. Potentially sensitising constituents include the active ingredients benzoic acid and salicylic acid, the preservative methylparaben, and yellow petrolatum.

– Irritation due to salicylic acid, lanette wax or inferior qualities of petrolatum may occur but are rare. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.
– Salicylic acid inhibits blood coagulation. This effect is unlikely to raise clinical issues following external use of Whitfield's cream. However, people using blood coagulation problems should only use salicylic acid containing preparations under close medical supervision.

Intoxication:
– Excessive or long-term use of salicylic acid containing preparations may cause systemic intoxication. This is unlikely to occur from using salicylic acid containing preparations on the skin, with the exception of long-term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Systemic intoxication is characterised by:
  • slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
  • more severe intoxication: excitation, confusion, fever and convulsions.
  • severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.

  When such effects occur, stop using the preparation immediately.

Additional information:
– The formula in this monograph differs from the Whitfield preparations generally used in Anglo-Saxon countries. The latter contain 6% benzoic acid and 3% salicylic acid. The 5%-5% formulation may be slightly more active.
– When basic cream is unavailable, emulsifying ointment can be used. More information about other vehicles is found in the monograph on Whitfield's ointment.
– When large quantities are prepared for stock storage, a freshly prepared basic cream should be used.

Whitfield's ointment 5%-5%
benzoic and salicylic acid ointment

Contains: benzoic acid 5% and salicylic acid 5% in emulsifying ointment.

Formulation
benzoic acid	5	g
salicylic acid	5	g
emulsifying ointment	90	g

Preparation:

1. Grind the benzoic acid and the salicylic acid. When sieves are available, sieve the benzoic acid and the salicylic acid, preferably through a 90 µm sieve.
2. Mix the benzoic acid with the salicylic acid.
3. Triturate this mixture with approximately 10 g emulsifying ointment until homogeneous.
4. Add the rest of the ointment gradually and mix until homogeneous.

Packaging:

– The ointment should be packed in a container which allows stirring. Whitfield's ointment should not be packed in collapsible tubes when the storage temperature may exceed 25 °C.
– When inhomogeneous, Whitfield's ointment should be mixed until homogeneous before dispensing.

Storage:

– Whitfield's ointment should preferably be stored below 25 °C.
– The ointment should preferably be used within 2 years.
– Expired ointment may be less effective.
– Whitfield's ointment may get inhomogeneous at temperatures higher than 25 °C. Inhomogeneity does not affect the ointment, but requires proper mixing before dispensing or use.

Therapy:

– For external use only.
– Whitfield's ointment combines a fungistatic activity with keratolytic properties. It is used for superficial skin infections caused by fungi, such as ringworm and athlete's foot. *Candida* species are insensitive.
– The cream is less hydrating than the ointment and is preferred in most cases.

Dose:

– The ointment should be applied twice daily in a thin layer to the affected parts of the skin. Treatment may take several weeks.

Instructions for use:

– Wash the skin with water and soap. Apply the ointment in a thin layer and rub it into the skin. Whitfield's ointment should only be applied to affected parts of the skin.
– Do not use past the expiry date. Use within 1 month after dispensing.

Precautions:

– When applied in a thick layer, the ointment has an occlusive, hydrating effect which should be avoided. Because of the occlusive effect, applying the ointment in skin folds should be avoided and the cream should be used instead.
– In small children, do not use the ointment on large parts of the body or for prolonged periods of time.
– Do not use the ointment for a patient who is known to be allergic to one of the constituents. When sensitisation reactions develop, stop using the ointment immediately.
– Ringworm and athlete's foot are highly contagious. If possible, close contacts (family, school) should be examined and treated if necessary.
– Good personal hygiene and careful drying of the skin are essential to prevent reinfection.

Pregnancy/breast feeding:
- Teratogenic effects of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans from external use of salicylic acid have not been described. Evaluate the benefit/risk ratio before using salicylic acid during pregnancy.
- Following external use salicylic acid is excreted in breast milk. No adverse effects in the child have been reported following the mother's external use of salicylic acid. Evaluate the benefit/risk ratio before using salicylic acid during breast feeding.

Side effects:
- Sensitisation may occur but is uncommon. Potentially sensitising constituents include the active ingredients benzoic acid and salicylic acid, and yellow petrolatum.
- Irritation due to lanette wax or to inferior qualities of white petrolatum may occur but are uncommon. When sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.
- Salicylic acid inhibits blood coagulation. This effect is unlikely to raise clinical issues following external use of Whitfield's ointment. However, people using blood coagulation problems should only use salicylic acid containing preparations under close medical supervision.

Intoxication:
- Excessive or long-term use of salicylic acid containing preparations may cause systemic intoxication. This is unlikely to occur from using salicylic acid containing preparations on the skin, with the exception of long-term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Systemic intoxication is characterised by:
  - slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
  - more severe intoxication: excitation, confusion, fever and convulsions.
  - severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.

  When such effects occur, stop using the preparation immediately.

Additional information:
- The formula in this monograph differs from the Whitfield preparations generally used in Anglo-Saxon countries. The latter contain 6% benzoic acid and 3% salicylic acid. The 5%-5% formulation may be slightly more active.
- When emulsifying ointment is unavailable, petrolatum with 10% wool fat can be used instead. This results in an ointment that is not washable, and may be more sensitising.
- Plain petrolatum as a vehicle for Whitfield's ointment is also possible, but results in a rather occlusive preparation. Occlusion may cause hydration of the infected skin and subsequent exacerbation of the disease.
- When large quantities are prepared for stock storage, a freshly prepared emulsifying ointment should preferably be used.

Zinc oil

zinc oxide liniment

Contains: 60% zinc oxide in vegetable oil

Formulation

zinc oxide	60	g
vegetable oil	40	g

Preparation:

1. When sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
2. Triturate the zinc oxide with the vegetable oil.
3. Mix until homogeneous.

Packaging:

- Zinc oil should be packed in airtight containers. As zinc oil attacks certain plastics, it should not be packed in plastic containers. Glass is most appropriate. The container should allow stirring of the zinc oil.
- When inhomogeneous, zinc oil should be mixed until homogeneous before dispensing from stock.

Storage:

- Zinc oil should preferably be stored below 40 °C.
- Zinc oil should preferably be used within 3 months.
- Upon storage the consistency of zinc oil changes gradually and the preparation becomes poorly spreadable and viscous. Therefore expired zinc oil is not easily applied to the skin.

Therapy:

- For external use only.
- Zinc oil has a general soothing effect and is used in various skin diseases.

Dose:

- Apply zinc oil several times daily to the skin.

Instructions for use:

- Zinc oil should be stirred before use.
- Zinc oil is not easily removed from the skin with water and soap. Rinse the skin with some vegetable oil before using water and soap.
- Do not use past the expiry date. Use within 1 month after dispensing.

Precautions:

- Zinc oil is unsuitable for hairy parts of the skin because it is difficult to remove.

Pregnancy/breast feeding:
– Harmful effects from external use of zinc oil have not been reported.

Side effects:
– Sensitisation may occur but is rare. The sensitisation potential depends largely on the type of oil used. If sensitisation reactions develop, stop using this preparation and do not use it again.

Additional information:
– Several pharmacopoeias recommend the addition of some oleic acid. This has a beneficial effect on the consistency of the preparation, but is not essential. Also, too much oleic acid results in a less stable preparation. Vegetable oils contain a certain amount of free oleic acid. The oleic acid content rises during storage, especially at higher temperatures. Oleic acid is therefore omitted from the formula.
– In this preparation, mineral oil (liquid paraffin) cannot be used instead of vegetable oil, because this will result in a preparation with a different therapeutic effect.

Zinc paste 50%
zinc oxide paste

Contains: 50% zinc oxide in petrolatum.

Formulation
zinc oxide	50	g
petrolatum	50	g

Preparation:
1. When sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
2. Melt the petrolatum over gentle heat.
3. Triturate the zinc oxide with the petrolatum.
4. Mix until no zinc oxide lumps are left and the preparation is homogeneous.

Packaging:
– Zinc paste does not require special packaging. A container with a wide opening is preferred as it is easier to take the paste out. Collapsible tubes are inappropriate as it may be difficult to remove the paste from them.

Storage:
– Zinc paste does not require special storage conditions.

– Zinc paste should preferably be used within 2 years.
– Expired pastes may be used as long as the consistency of the preparation remains satisfactory.

Therapy:

– For external use only.
– Zinc paste has good protective properties without being very occlusive. Due to its high powder content, zinc paste may have a drying effect on the skin. It is used in the healing process of clean ulcers, e.g., in leprosy.
– As the zinc oxide particles in the paste reflect sunlight, zinc paste is an effective sun blocking preparation.
– Zinc paste is also used as a vehicle for tar and dithranol.

Dose:

– Apply zinc paste several times daily to the skin.

Instructions for use:

– Zinc paste should be applied to the skin or the clean ulcer in a layer just thick enough to provide adequate protection. The paste layer may be covered with a loose bandage.
– Zinc paste is very difficult to remove from the skin. It is therefore unsuitable for hairy parts of the skin. To remove zinc paste from the skin, rinse with some vegetable oil before using water and soap.
– Do not use past the expiry date. Use within 3 months after dispensing.

Pregnancy/breast feeding:

– Harmful effects from external use of zinc paste have not been reported.

Side effects:

– Yellow petrolatum may cause sensitisation reactions. Sensitisation reactions to white petrolatum are very rare. However, inferior quality white petrolatum may cause irritation. If sensitisation or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information:

– The formula for zinc paste was adapted from a formula used in many pharmacopoeias. The original formula contains 25% zinc oxide, 25% starch and 50% paraffins. Starch is inappropriate for hot and humid climates because it is usually highly contaminated with micro-organisms. The paste with 50% zinc oxide has the same general characteristics as the original formula.

13 Raw material monographs

All raw materials that are used in the dermatological preparations of the formulary are listed in this chapter. Each monograph has the same format and may contain the following headings:

Title

Synonyms

Description:
A description of appearance, colour and smell.

Qualities/varieties:
Information on the available qualities, their differences and suitability for the preparations included in the formulary.

Density:
The density of the material (at 20 °C, for fluids only), to convert weight to volume and volume to weight.

Packaging:
Information on packaging requirements.

Storage:
Information on storage requirements, stability, signs of degradation (if any), and risks associated with using expired raw materials. The term "should" is used to specify necessary requirements, while "should preferably" indicates strongly recommended procedures. When indicated that a raw material should be kept cool, the recommended storage temperature is below 15 °C.

Hazards/toxicity:
Information on special hazards (fire and explosive hazards), systemic and local toxicity, information on how to treat a person after accidental skin or eye contact, accidental ingestion, and, if relevant, information on environmental hazards.

Aluminium magnesium silicate

Magnesium aluminium silicate, saponite.

Description:
Aluminium magnesium silicate is an odourless, creamy-white powder or small flakes.

Qualities/varieties:
Aluminium magnesium silicate is available in various grades. For dermatological preparations a pharmaceutical grade is required. Aluminium magnesium silicate is branded under various trade names, such as Veegum® (UK, US), Dianeusine® (F) and Sicco-gynaedron® (BRD).

Packaging:
Aluminium magnesium silicate does not require special packaging.

Storage:
Aluminium magnesium silicate does not require special storage conditions and has a practically indefinite shelf life.

Hazards/toxicity:
Inhalation of dust particles should be avoided.

Ascorbic acid

Vitamin C

Description:
Ascorbic acid consists of odourless and colourless crystals or a white to slightly yellowish powder.

Packaging:
Ascorbic acid should be packed in airtight, non-metallic containers, which protect the ascorbic acid from exposure to direct sunlight.

Storage:
Ascorbic acid should be protected from exposure to direct sunlight. It should be used before the expiry date. Expired ascorbic acid is less effective.

Bentonite

Mineral soap, soap clay, wilkinite.

Description:
Bentonite is an odourless fine, greyish-white powder with a yellowish tint, or pale-buff coloured.

Qualities/varieties:
Bentonite is available in different qualities. For dermatological preparations a pharmaceutical grade is required.

Packaging:
Bentonite should be packed in airtight containers.

Storage:
No special storage conditions are required. The shelf life of bentonite is practically indefinite. Bentonite may absorb moisture from the air. It usually contains bacterial spores. When bentonite gets wet, the microbial count is likely to increase.

Hazards/toxicity:
Inhalation of dust particles should be avoided.

Benzoic acid

Description:
Benzoic acid consists of colourless feathery crystals, white scales or a white powder with a slight characteristic odour.

Packaging:
Benzoic acid should be packed in airtight containers.

Storage:
Benzoic acid does not require special storage conditions. It should preferably be used before the expiry date. Expired benzoic acid may be less effective.

Hazards/toxicity:
Benzoic acid is relatively non-toxic. Avoid inhalation of dust particles, which are irritating.

Benzyl benzoate

Description:
Benzyl benzoate is a clear colourless oily liquid with a faint characteristic odour. At temperatures below 18 °C it crystallises.

Density:
Benzyl benzoate: 1 ml = 1.12 g 1 g = 0.89 ml

Packaging:
Benzyl benzoate should be packed in well filled, airtight containers, which protect against exposure to light.

Storage:
Benzyl benzoate should preferably be stored below 40 °C. Benzyl benzoate should preferably be used before the expiry date. Expired benzyl benzoate may be less effective.

Hazards/toxicity:
Benzyl benzoate causes central nervous system depression after ingestion, leading to convulsions. After accidental ingestion induce vomiting with syrup of ipecacuanha. Diazepam injections can be used to treat convulsions.

Calamine

Description:
Calamine is a reddish-brown amorphous powder. It is odourless.

Qualities/varieties:
In many pharmacopoeias, for example in the *British Pharmacopoeia*, calamine is defined as a basic zinc carbonate, coloured with ferric oxide. Other pharmacopoeias specify it differently, i.e., the *United States Pharmacopeia* defines calamine as zinc oxide coloured with ferric oxide. Both qualities are equivalent. Calamine of pharmaceutical quality does not require grinding or sieving.

Packaging:
Calamine should be packed in an airtight container.

Storage:
Calamine should be kept dry. As long as calamine is kept dry, it has a practically indefinite shelf life.

Hazards/toxicity:
Inhalation of calamine should be avoided.

Chlorhexidine diacetate

Description:
Chlorhexidine diacetate is a white to pale-cream coloured, almost odourless crystalline powder.

Packaging:
Chlorhexidine diacetate should be packed in airtight containers, which protect against exposure to light. Cork closures should not be used.

Storage:
Chlorhexidine diacetate does not require special storage conditions. It should be protected from light. Chlorhexidine diacetate should preferably be used before the expiry date. Expired chlorhexidine may be less effective.

Hazards/toxicity:
Chlorhexidine diacetate is poorly absorbed from the gastro-intestinal tract and is therefore relatively non-toxic. After accidental ingestion induce vomiting with syrup of ipecacuanha.

Chlorhexidine digluconate stock solution 20%

Description:
Chlorhexidine digluconate stock solution 20% is a colourless to pale straw-coloured almost odourless liquid. It may be clear or slightly opalescent.

Qualities/varieties:
A commercial chlorhexidine digluconate 5% solution is available in some countries. It contains a nonionic surfactant and a red colouring agent. Such solutions offer no advantages for general use. The chlorhexidine digluconate stock solution 20% is recommended.

Density:
Chlorhexidine digluconate stock solution 20%: 1 ml = 1.06 g 1g = 0.94 ml

Packaging:
Chlorhexidine digluconate stock solution 20% should be packed in airtight containers, which protect against exposure to light.

Storage:
Chlorhexidine digluconate stock solution 20% should preferably be kept below 25 °C. It should be protected from light. It should be used before the expiry date. Expired chlorhexidine digluconate stock solution 20% is less effective.

Hazards/toxicity:
Chlorhexidine digluconate is poorly absorbed from the gastro-intestinal tract and is therefore relatively non-toxic. After accidental ingestion induce vomiting with syrup of ipecacuanha.

Citric acid monohydrate

Hydrous citric acid, acidum citricum monohydricum, E330

Description:
Citric acid monohydrate is a white crystalline powder, or consists of colourless, odourless crystals.

Qualities/varieties:
Citric acid monohydrate is widely used in food. It is also available in an anhydrous form. This attracts water to form the monohydrate. Formerly, citric acid without specification denoted the anhydrous form.

Packaging:
Citric acid monohydrate should be packed in airtight containers.

Storage:
Citric acid monohydrate should be kept dry.

Coal tar

pix lithantracis, pix carbonis

Description:
Tar is a dark brown to black viscous liquid with a characteristic smell. It consists of a complex mixture.

Qualities/varieties:
Tars are obtained from the destructive distillation of coal (coal tar, pix lithantracis, pix carbonis) or wood (wood tar, pine tar, pix pini, pix liquida, Stockholm tar). Coal tar is more effective than wood tar, but it may cause phototoxic reactions. Coal tar has a low sensitisation potential. In contrast, wood tar is less effective, has a higher sensitisation potential, but does not cause phototoxic reactions. To differentiate between the two types of tar, shake some tar with water. The water will show an acidic reaction in the case of wood tar, and an alkaline reaction in the case of coal tar. Both coal tar and wood tar show variations in composition, which are comparable regarding activity and safety. Coal tar is preferred over wood tar because it is more effective and less sensitising.

Packaging:
Tars should be packed in airtight containers.

Storage:
Tars should preferably be kept cool. They should preferably be used before the expiry date. Expired tars may be less effective due to evaporation of volatile constituents. Increased toxicity is unlikely to occur.

Hazards/toxicity:
Tars contain various toxic, irritating and carcinogenic constituents. While handling coal tar, avoid contact with the skin and do not inhale vapours. After accidental contact with the skin, wash with water and soap.

Dithranol

anthralin, dioxyanthranol, 1,8 dihydroxy 9 anthron

Description:
Dithranol is a yellow to yellowish-brown crystalline powder.

Packaging:
Dithranol should be packed in airtight containers, which protect against exposure to light.

Storage:
Dithranol should preferably be kept cool. It should be used before the expiry date. Expired dithranol is less effective. It is unclear whether expired dithranol has increased toxicity. Degraded dithranol shows a discolouration to purple-brown or black.

Hazards/toxicity:
Dithranol is a powerful irritant. While handling dithranol, avoid contact with the skin and the eyes. After accidental contact with dithranol rinse the skin or the eyes immediately with water.

Gentian violet

CI basic violet 3, colour index no 42555, crystal violet, hexamethylpararosaniline chloride, methylrosaniline chloride, pyoctaninum caeruleum

Description:
Gentian violet consists of crystals with a greenish-bronze colour. It is odourless or almost odourless.

Qualities/varieties:
Gentian violet consists of a mixture of triphenylmethane dyes. Various qualities are available containing different homologues. The pure dye is preferred to prepare gentian violet solution.

Packaging:
Gentian violet should be packed in airtight containers.

Storage:
Gentian violet does not require special storage conditions. It is quite stable and can be used as long as it has a good appearance and colour.

Hazards/toxicity:
Undissolved crystals, or solutions with a strength of more than 1% gentian violet are irritating on the skin and may cause necrotic skin reactions. After accidental contact with the skin, rinse immediately with a lot of water. After contact with the eyes, rinse immediately with a lot of water and request medical advice. After ingestion of gentian violet, local corrosion of the gullet and stomach may result. Request medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha. Gentian violet is a very staining substance. It is a suspected carcinogenic agent, but this is unproven.

Glycerin
glycerol, glycerol 80% or 85% in water

Description:
Glycerin is a clear syrupy liquid that should be almost colourless and almost odourless.

Qualities/varieties:
Glycerin is miscible with water. The nomenclature differs internationally and is not always clear. In some countries the name glycerol is used for the pure substance without water, while glycerin describes a solution of 80% or 85% in water. However, internationally the names glycerin, glycerin and glycerol are often used as synonyms. All of these varieties can be used for calamine lotion.

Density:

Pure glycerol (free from water):	1 ml = 1.26 g	1 g = 0.79 ml
85% glycerin:	1 ml = 1.22 g	1 g = 0.82 ml

Packaging:
Glycerin should be packed in airtight containers.

Storage:
Glycerin should preferably be kept at room temperature.

At low temperatures it turns into a solid. To melt it again, warm gently to a temperature slightly above 20 °C. Glycerin should preferably be used before the expiry date. It can be used past the expiry date, as long as the appearance is satisfactory.

Hazards/toxicity:
Glycerin is relatively non-toxic. After accidental ingestion of very large doses it may cause headache, nausea and thirst.

Hydrocortisone acetate

Description:
Hydrocortisone acetate consists of a white or almost white powder.

Packaging:
Hydrocortisone acetate should be packed in airtight containers, which protect against exposure to light.

Storage:
Hydrocortisone acetate does not require special storage conditions, other than protection from light. Hydrocortisone acetate should preferably be used before the expiry date. Expired hydrocortisone acetate may be less effective.

Hazards/toxicity:
After accidental ingestion request medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

Industrial methylated spirit
alcohol

Description:
Industrial methylated spirit is a colourless liquid with a characteristic odour.

Qualities/varieties:
Methylated spirit is alcohol mixed with methanol and possibly other ingredients to make it toxic and therefore unsuitable for human consumption.
Methylated spirits containing pyridine can be recognised by their smell. Mineralised methylated spirit, which is generally used as household spirit, has a characteristic blue colour. It can also be recognised by the opaque

solution after mixing with water. Spirits containing pyridine or benzene should not be used for any drug preparations.

For dermatological preparations, industrial methylated spirit without pyridines or benzene is suitable. For iodine tincture, however, a special quality should be used, that is free from acetone and other ketones.

Spirit is methylated for reasons of taxation. When a government is willing to exempt pure pharmaceutical ethanol from taxes, this ethanol can also be used. The alcohol content of the spirit is important. 95% industrial methylated spirit, also known as 66 OP, is suitable. If the spirit has to be diluted, weaker spirits can be used, for which the amount required has to be calculated carefully. This calculation is done with the following formula: amount to be diluted with water to 100 g = 100 x percentage wanted/percentage available. An example: you want to prepare a 70% spirit. Your industrial methylated spirit has a strength of 90%. You should dilute 100 x 70/90 g = 78 g of the spirit with water to 100 g to obtain the right dilution. Dilution by volume is less accurate because of volume contraction (the volume of the resulting solution is less than the sum of the original volumes).

Packaging:
Industrial methylated spirit should be packed in an airtight container.

Storage:
Industrial methylated spirit should be kept as cool as possible, preferably below 15 °C.

Hazards/toxicity:
Industrial methylated spirit is flammable. Ethanol is toxic when ingested in large quantities. The methanol used to make the spirit unsuitable for human consumption is even more toxic and may cause blindness. Upon ingestion request medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha and give a 5% sodium bicarbonate solution in water orally.

Iodine

Description:
Iodine consists of greyish-violet to bluish-black plates or crystals with a metallic shine and an irritant odour. Iodine is volatile at 20 °C.

Packaging:
Iodine should be packed in airtight containers made of glass or earthenware.

Storage:
Iodine should preferably be kept cool. It may evaporate if the container is not closed well.

Hazards/toxicity:
Iodine forms strongly irritant substances with acetones and other ketones. Iodine is irritant to the skin and the eyes. While handling iodine, avoid contact with the skin and the eyes. Iodine is strongly irritant and toxic when ingested. After accidental ingestion request medical advice. While waiting for a doctor, give milk and starch first, and then induce vomiting with syrup of ipecacuanha. When starch is unavailable, sodium thiosulphate is also appropriate.

Lanette wax

cera emulsificans, emulsifying wax.

Description:
Lanette wax is an almost white or pale yellow waxy solid or flakes. It has a faint characteristic odour.

Qualities/varieties:
Lanette wax is both a trade name for a number of mixtures of fatty alcohols and other constituents, and a non-official name for some of these mixtures. The *British Pharmacopoeia* uses the name 'emulsifying wax' for a mixture of 90% cetostearyl alcohol and 10% sodium lauryl sulphate. This is equivalent to lanette wax SX, a branded product. The *British Pharmacopoeia* also indicates the preparation method. Another commonly used mixture contains cetostearyl alcohol 90% and sodium cetostearyl sulphate 10%. This is available as lanette wax N. Lanette wax SX and other mixtures of fatty alcohols with sulphonated fatty alcohols are widely used in creams. Although the mixtures are similar and suitable for creams, lanette wax SX is preferred because it results in the most stable cream. The non-official name 'lanette wax' is used in this formulary instead of emulsifying wax, to avoid confusion with the term emulsifying ointment.

Packaging:
Lanette waxes usually are stable and do not require special packaging materials. A particular product, however, can require special packaging because it is sensitive to light or to oxygen from the air. Such products should therefore be stored in airtight containers, which also protect against exposure to light, unless otherwise indicated in the specifications.

Storage:
Lanette wax should preferably be kept below 25 °C. It melts at higher temperatures and forms a solid mass upon resolidification. Lanette wax should preferably be used before the expiry date. Expired lanette wax can be used as long as it has a satisfactory appearance and smell.

Lindane

gamma benzene hexachloride, gamma BHC, gamma HCH, gamma hexachlorocyclohexane, gammexane.

Description:
Lindane is a white crystalline powder which may have a slight odour.

Packaging:
Lindane should be packed in airtight containers, which protect against exposure to light.

Storage:
Lindane should be protected from light, otherwise no special storage conditions are required. Lindane should preferably be used before the expiry date. Expired lindane may be less effective.

Hazards/toxicity:
Lindane is a toxic substance with general stimulating effects on the nervous system. While handling lindane, avoid contact with the skin and the eyes. Accidental ingestion may cause restlessness, muscle spasms and seizures. Request medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha as soon as possible. Diazepam injections can be used to treat seizures. Treatment otherwise is supportive and includes assistance of respiration.
Lindane is harmful for the environment. Discarded lindane should be treated as chemical waste (chlorinated pesticides).

Liquid paraffin

liquid petrolatum, oleum vaselini, vaselinum liquidum, white mineral oil.

Description:
Liquid paraffin is a clear oily liquid. It is colourless and odourless or almost odourless.

Qualities/varieties:
Liquid paraffin is a complex mixture of liquid hydrocarbons. Its composition differs according to the source of the petroleum. In most pharmacopoeias liquid paraffin designates the heavy quality. Both heavy and light liquid paraffin are suitable for dermatological preparations. The heavy variety is preferred, because it leads to more stable preparations.

Density:
The density of liquid paraffin varies with variety and composition. Calculations should preferably be based upon the exact density given in the product specifications.

Heavy variety:	1 ml = 0.83 - 0.89 g	1 g = 1.12 -1.20 ml
Light variety:	1 ml = 0.82 - 0.88 g	1 g = 1.13 -1.22 ml

Packaging:
Liquid paraffin should be packed in airtight containers, which protect against exposure to light.

Storage:
Liquid paraffin should be protected from light, otherwise no special storage conditions are required. Liquid paraffin is stable and can be used as long as it has a good appearance and smell.

Liquefied phenol

phenol aqueux, phenol liquefactum.

Description:
Liquefied phenol is a colourless liquid with a characteristic odour. It may have a slight pink colour.

Qualities/varieties:
Liquefied phenol is a solution of water in phenol. It is used in various strengths, ranging from 77% to 90% phenol. These are all suitable to prepare calamine lotion.

Density:
Liquefied phenol : 1 ml = 1.05 g 1 g = 0.95 ml

Packaging:
Liquefied phenol should be packed in airtight containers, which protect against exposure to light.

Storage:
Liquefied phenol should preferably be kept cool. It should be protected from light. Degraded phenol has a pink colour. Slightly pink coloured phenol can still be used. Degraded phenol is less effective or ineffective.

Hazards/toxicity:
Phenol is corrosive. Phenol itself and strong solutions (10% and higher) are irritant on the skin and the eyes and may cause chemical burns. Phenol is absorbed through the skin. While handling phenol, avoid contact with the skin and the eyes. After accidental contact remove contaminated clothes and wash the skin with a lot of water. After contact with the eyes rinse immediately with plenty of water. After ingestion, phenol causes local corrosion with intense pain, nausea and vomiting. These effects are followed by depression of the central nervous system, death may result from respiratory failure. Doses of more than 1 g phenol may be fatal.
After accidental ingestion request medical advice. Empty the stomach as soon as possible, preferably with gastric lavage. This should be done carefully to prevent causing even more damage to the stomach and gullet. Give 50 ml castor oil, or bring castor oil into the stomach to slow down absorption. Treatment otherwise is supportive: keep the patient warm, treat acidosis and assist respiration.
Chronic exposure to phenol and other phenolic compounds may result in chronic phenol intoxication. Weight loss, loss of appetite, dark urine and pain in the limbs are the most common symptoms of chronic phenol poisoning. Patients usually recover when exposure to phenolic compounds ends.

Methylparaben

methyl hydroxybenzoate, methylis oxybenzoas, methyl para-hydroxybenzoate, MOB, E218.

Description:
Methylparaben consists of a fine white crystalline powder or colourless crystals. It may have a slight odour.

Packaging:
The packaging materials should protect methylparaben from exposure to light.

Storage:
Methylparaben should be protected from light, otherwise no special storage conditions are required. Methylparaben should preferably be used before the expiry date. Expired methylparaben may be less effective.

Hazards/toxicity:
After accidental ingestion induce vomiting with syrup of ipecacuanha.

Octinoxate

parsol MCX, OMC, octyl methoxycinnamate, ethylhexyl methoxycinnamate, 2-ethylhexyl (2E)-3-(4-methoxyphenyl)prop-2-enoate

Description:
Octinoxate is a clear to pale yellow viscous liquid insoluble in water.

Density:
Octinoxate: 1 ml = 1.01 g

Packaging:
Octinoxate should be packed in airtight containers, which protect against exposure to light.

Storage:
Octinoxate should be protected from light. It should preferably be used before the expiry date. Expired octinoxate may be less effective.

Hazards/toxicity:
Octinoxate is well tolerated. There are some concerns about risks during pregnancy. Therefore, pregnant women should avoid handling octinoxate.

Petrolatum

paraffinum molle, petroleum jelly, soft paraffin, vaseline.

Description:
Petrolatum is a white to pale yellow translucent unctuous mass. It is almost odourless.

Qualities/varieties:
Petrolatum is a complex mixture of solid and liquid hydrocarbons. Its exact composition varies according to the source and manufacturer. 'Natural' petrolatum has a yellow colour. It contains various constituents which rarely cause sensitisation reactions. In white petrolatum these constituents were degraded with a bleaching agent. Inferior qualities of white petrolatum may still contain residues of the bleaching agents, causing skin irritation. Both qualities, natural and white petrolatum, are used in dermatological preparations. Vaseline® is a cosmetic trade mark in some countries, including Great Britain. The name is also widely used for petrolatum.

Packaging:
Petrolatum should be packed in a container, which protect against exposure to light.

Storage:
Petrolatum should be protected from light. It should preferably be kept cool. At temperatures higher than 25 °C separation of oil occurs. Petrolatum should be homogenised before dispensing or use. Petrolatum is stable and can be used as long as its appearance remains satisfactory.

Phenol

carbolic acid, hydroxybenzene.

Description:
Phenol consists of colourless crystals or a crystalline mass. It turns pink upon storage. It has a characteristic odour.

Packaging:
Phenol should be packed in airtight containers, which protect against exposure to light.

Storage:
Phenol should preferably be kept cool. It melts at higher temperatures. Phenol should be protected from light. Degraded phenol has a pink colour. Slightly pink coloured phenol can still be used. Degraded phenol is less effective or ineffective.

Hazards/toxicity:
Phenol is corrosive. Phenol itself and strong solutions (10% and higher) are irritant to the skin and the eyes and may cause chemical burns. Phenol is absorbed through the skin. While handling phenol, avoid contact

with the skin and the eyes. After accidental contact remove contaminated clothes and wash the skin with a lot of water. After contact with the eyes rinse immediately with plenty of water. After ingestion phenol causes local corrosion with intense pain, nausea and vomiting. These effects are followed by depression of the central nervous system, death may result from respiratory failure. Doses of more than 1 gram may be fatal.
After accidental ingestion request medical advice. Empty the stomach as soon as possible, preferably with gastric lavage. This should be done carefully to prevent causing even more damage to the stomach and gullet. Give 50 ml castor oil, or bring castor oil in the stomach to slow down absorption. Treatment otherwise is supportive: keep the patient warm, treat acidosis and assist respiration.
Chronic exposure to phenol and other phenolic compounds may result in chronic phenol intoxication. Weight loss, loss of appetite, dark urine and pain in the limbs are the most common symptoms of chronic phenol poisoning. Patients usually recover when exposure to phenolic compounds ends.

Polysorbate 80

polyoxyethylene 20 sorbitan monooleate, sorbimacrogol oleate 300.

Description:
Polysorbate 80 is a clear brownish-yellow oily liquid with a faint characteristic odour.

Packaging:
Polysorbate 80 should be packed in airtight containers, which protect against exposure to light.

Storage:
Polysorbate 80 should be protected from light, otherwise no special storage conditions are required. It can be used as long as its appearance and smell remain satisfactory.

Potassium iodide

kalium iodidum

Description:
Potassium iodide consists of transparent or somewhat opaque crystals or a white powder. It is odourless and colourless.

Packaging:
Potassium iodide should be packed in airtight containers, which protect against exposure to light.

Storage:
Potassium iodide should be protected from exposure to light, otherwise no special storage conditions are required. Iodide may be released, which results in a yellow to brown discolouration. Discoloured potassium iodide can still be used to prepare iodine solutions for external use, but not for systemic preparations.

Hazards/toxicity:
Potassium iodide is readily absorbed from the stomach after ingestion. After accidental ingestion request medical advice. While waiting for a doctor induce vomiting as soon as possible with syrup of ipecacuanha.

Potassium permanganate
kalium hypermanganicum

Description:
Potassium permanganate consists of dark purple to black crystals. It is odourless.

Packaging:
Potassium permanganate should be stored in airtight containers, which protect against exposure to light. The containers should not be made of, or contain, organic materials such as paper or cork.

Storage:
Potassium permanganate should be protected from light, otherwise no special storage conditions are required. It should preferably be used before the expiry date. Partially degraded potassium permanganate shows a brown discolouration. The degradation of potassium permanganate in solutions is increased by the degradation products. Degraded potassium permanganate is not effective. Expired potassium permanganate still can be used, but it dissolves even more slowly than the original material. It can be used, but only when complete dissolution can be guaranteed. This means that the solution needs to be filtered. In the presence of organic materials, potassium permanganate degrades rapidly. Therefore, the solution should not be filtered over organic materials such as cotton wool or paper. A glass filter is suitable.
The correct strength of a solution prepared with partially degraded potassium permanganate can only be determined on the colour. Solutions prepared with expired potassium permanganate contain degradation products causing a brownish colour through the purple colour, and are less stable.

Hazards/toxicity:
Potassium permanganate forms explosive mixtures with some organic substances. It is used for the production of firework and explosives.
Potassium permanganate crystals and solutions are very irritating and may cause chemical burns. While handling potassium permanganate, avoid contact with the skin and the eyes. After accidental contact with the skin remove contaminated clothes and rinse with a lot of water. After accidental contact with the eyes, immediately rinse with a lot of water. A sodium thiosulphate solution is suitable to inactivate potassium permanganate.

Accidental ingestion causes nausea and vomiting. Request medical advice. While waiting for a doctor, give milk immediately to slow down absorption. A sodium thiosulphate solution, when given immediately, is useful to inactivate the potassium permanganate. Treatment otherwise is supportive and includes keeping the patient warm and assisting respiration. Intoxication with potassium permanganate results in liver and kidney damage, and also affects the cardiovascular system. The fatal dose is assumed to be approximately 10 g. Death may occur up to 1 month after intoxication.
Potassium permanganate is harmful for the environment. Discarded potassium permanganate should be treated as chemical waste (heavy metals).

Povidone Iodine

polyvinylpyrrolidone-Iodine, PVP-Iodine.

Description:
Povidone iodine is a yellowish-brown powder with a slight, characteristic odour.

Qualities/varieties:
Povidone iodine is a complex of iodine with povidone. It contains 9-12% of available iodine.

Packaging:
Povidone iodine should be packed in airtight containers.

Storage:
Povidone iodine should be stored in airtight containers. Expired povidone iodine may have lost iodine by evaporation and may be less effective.

Hazards/toxicity:
Povidone iodine has the same effects as iodine itself, but they are less severe. Iodine forms strongly irritant substances with acetones and other ketones. Iodine is irritant to the skin and the eyes. While handling iodine, avoid contact with the skin and the eyes. Iodine is strongly irritant and toxic when ingested. After accidental ingestion request medical advice. While waiting for a doctor, give milk and starch first, and then induce vomiting with syrup of ipecacuanha. When starch is unavailable, sodium thiosulphate is also appropriate.

Salicylic acid

2-hydroxybenzoic acid, acido ortoxicobenzoico.

Description:
Salicylic acid consists of colourless feathery crystals or a white crystalline powder. It is odourless, but dust particles irritate the nose.

Qualities/varieties:
Salicylic acid is available in various particle sizes. For dermatological preparations a particle size of about 90 µm is preferred. When a larger particle size is at hand, it should be grounded and preferably sieved before usage. The exception to this rule is the preparation of salicylic acid solution, for which all particle sizes are suitable.

Packaging:
Salicylic acid should be packed in airtight containers.

Storage:
Salicylic acid requires no special storage conditions. Salicylic acid should preferably be used before the expiry date, but expired salicylic acid can be used as long as the appearance and smell of the product remain satisfactory. The particle size of expired salicylic acid may have changed. Therefore, expired salicylic acid should always be sieved and, if necessary, grounded before use.

Hazards/toxicity:
Avoid inhaling salicylic acid dust, which is irritating.
Salicylic acid is moderately toxic. After ingestion of large amounts of salicylic acid, induce vomiting with syrup of ipecacuanha. Request medical advice when relatively large amounts of salicylic acid have been ingested.

Silver nitrate

argenti nitras, nitrato de plata

Description:
Silver nitrate consists of colourless crystals or a white crystalline powder. It is odourless.

Packaging:
Silver nitrate should be packed in airtight, non-metallic containers, which protect against exposure to light.

Storage:
Silver nitrate should be protected from light, otherwise no special storage conditions are required. Degraded silver nitrate is less effective or ineffective. Degraded silver nitrate shows a discolouration to grey or greyish

black. Silver nitrate with a slightly greyish colour can still be used. Stronger coloured silver nitrate should be discarded.

Hazards/toxicity:
Silver nitrate crystals and strong solutions are caustic to the skin and the eyes. Avoid contact with the skin and the eyes while handling silver nitrate. After accidental contact remove contaminated clothes and rinse with a lot of water. Sodium thiosulphate solution can be used to inactivate silver nitrate.
Request medical advice after accidental ingestion of silver nitrate or silver nitrate solutions. While waiting for a doctor, give a sodium chloride solution (table salt, about 1%) immediately and repeatedly. To empty the stomach induce vomiting with syrup of ipecacuanha. When available, gastric lavage is preferred. Give sodium sulphate as a purgative. When an analgesic is needed for pain treatment, paracetamol (also known as acetaminophen) is preferred over aspirin.
Silver nitrate is harmful for the environment. Discarded silver nitrate should be treated as chemical waste (heavy metals).

Sodium dihydrogen phosphate

monobasic sodium phosphate, sodium acid phosphate, sodium biphosphate, sodium dihydrogen orthophosphate

Description:
Sodium dihydrogen phosphate consists of odourless colourless crystals or white crystalline powder.

Qualities/varieties:
Sodium dihydrogen phosphate can absorb different amounts of crystal water. In this formulary the anhydrous variety is used. Other varieties can be used to prepare povidone iodine solution, provided the resulting pH is measured and adjusted if necessary. The sodium dihydrogen phosphate cannot, however, be replaced by sodium monohydrogen phosphate (also called: disodium phosphate), because this does not produce the proper pH value for the povidone iodine solution.

Packaging:
Sodium dihydrogen phosphate should be packed in airtight containers.

Storage:
Sodium dihydrogen phosphate should be kept dry.

Sodium iodide

natrium iodidum

Description:
Sodium iodide consists of transparent or somewhat opaque crystals or a white powder. It is odourless and colourless.

Packaging:
Sodium iodide should be packed in airtight containers, which protect against exposure to light.

Storage:
Sodium iodide should be protected from exposure to light, otherwise no special storage conditions are required. Iodide may be released, which results in a yellow to brown discolouration. Discoloured sodium iodide can still be used to prepare iodine solutions for external use, but not for systemic preparations.

Hazards/toxicity:
Sodium iodide is readily absorbed from the stomach after ingestion. After accidental ingestion induce vomiting as soon as possible with syrup of ipecacuanha. Request medical advice.

Sodium thiosulphate

sodium hyposulphite

Description:
Sodium thiosulphate consists of colourless crystals or a crystalline powder. It is almost odourless.

Qualities/varieties:
In addition to pharmaceutical qualities, various technical qualities of sodium thiosulphate are also available. It is for example used as fixation agent in photography. Such technical qualities can be used to prepare sodium thiosulphate solutions, provided they do not contain any technical additives. When technical qualities are used, take care to prevent accidental mix-ups with pharmaceutical qualities of sodium thiosulphate, which are used as antidotes in parenteral preparations.

Packaging:
Sodium thiosulphate should be packed in airtight containers.

Storage:
Sodium thiosulphate does not require special storage conditions. It should preferably be used before the expiry date. Expired sodium thiosulphate may be less effective.

Sulphur

Description:
Precipitated sulphur is a pale yellow, greyish-yellow or greenish-yellow, amorphous or microcrystalline powder, that should be odourless and tasteless.

Qualities/varieties:
Different forms of sulphur are known in pharmacy:
Precipitated sulphur (milk of sulphur, lac sulphuris) is a fine powder free from grittiness.
Sublimed sulphur (flour of sulphur) is a gritty powder. Sublimed sulphur has, in contrast to precipitated sulphur, a characteristic odour.
Washed sulphur is a special quality of sublimed sulphur. It is a fine, odourless, crystalline powder.
Because of its small particle size, precipitated sulphur is most effective in dermatological preparations. When this quality is unavailable, washed sulphur can be used. Sublimed sulphur is less effective and should only be used when precipitated or washed sulphur cannot be obtained.

Packaging:
Sulphur does not require special packaging.

Storage:
Sulphur does not require special storage conditions. The risks associated with the use of expired sulphur are considered low. Precipitated and washed sulphur should be odourless.

Hazards/toxicity:
Sulphur has a low general toxicity. It can be used as an ingredient for fireworks and explosives, but pure sulphur is not explosive.

Titanium dioxide

CI pigment white 6, Colour Index No. 77891, E171

Description:
Titanium dioxide is a white or almost white powder. It is odourless.

Qualities/varieties:
Titanium dioxide is widely used as a pigment. Technical qualities may contain various technical additives. In addition, they may have other particle size characteristics. A pharmaceutical quality is therefore preferred.

Packaging:
Titanium dioxide should be stored in airtight containers.

Storage:
Titanium dioxide does not require special storage conditions. It has a practically indefinite shelf life.

Hazards/toxicity:
Inhalation of dust particles should be avoided.

Trisodium citrate
natrii citras, sodium citrate

Description:
Trisodium citrate consists of colourless crystals or a white crystalline powder. It is odourless. It is slightly deliquescent in moist air and slightly efflorescent in warm dry air.

Qualities/varieties:
The World Health Organization recommends trisodium citrate dihydrate in oral rehydration solutions, because of its wide availability. This quality is adequate for calamine lotion. The anhydrate can also be used, for which no corrections of quantities in the recipe are required. When other hydrates are used, the quantities in the recipe require correction to account for the differences in molecular weight.

Packaging:
Trisodium citrate should be packed in airtight containers.

Storage:
No special storage conditions are required. Trisodium citrate should preferably be used before the expiry date. Expired trisodium citrate may be less effective. This can still be used to prepare calamine lotion, as long as the resulting lotion can be easily poured from a medicine bottle.

Urea
carbamide

Description:
Urea consists of colourless crystals or pellets, or a white crystalline powder. It is almost odourless.

Packaging:
Urea should be packed in airtight containers.

Storage:
Urea should preferably be kept cool. Degraded urea has the smell of ammonia. It can still be used but may be less effective.

Hazards/toxicity:
Urea is relatively non-toxic. After accidental ingestion nausea and vomiting may occur.

Vegetable oil

Description:
Vegetable oils are oily liquids. Most of them have some characteristic odour. Their colours range from colourless to yellow or brown.

Qualities/varieties:
A great number of vegetable oils are used in foods. Their characteristics differ according to the plant source and manufacturing process. All vegetable oils which are suitable for human consumption can be used to prepare dermatologicals, except oils with a high sensitisation potential, such as sesame oil. Various native oils may also have a high sensitisation potential. When sensitisation reactions occur from the application of zinc oil, switch to some other vegetable oil.

Packaging:
Vegetable oils should be packed in airtight bottles, which protect against exposure to light.

Storage:
Vegetable oils should be protected from light, otherwise no special storage conditions are required. Native oils generally do not carry expiry dates. They should be judged upon their smell and appearance. Older oils, especially after exposure to light and oxygen from the air, have a high acid content. When used in zinc oil, its stability will be poor. When the stability of zinc oil is problematic, switch to other oils or more recently manufactured ones.

Water

Description:
Water is a clear colourless and odourless liquid.

Qualities/varieties:
Water can be obtained from various sources, such of as rain, groundwater, surface areas and the tap. The water for dermatological preparations should be at least potable quality. The water to prepare dermatologicals should always be freshly boiled and cooled. This means that it should be heated until it boils, and after 1 minute boiling is allowed to cool down under coverage. It should be used within 1day. For further information on safe water see the appendix.

Density:
Water: 1 g = 1 ml

Storage:
Water should not be kept as it is readily contaminated with micro-organisms. Water that needs to be stored requires preservation, for example by chlorination.

Zinc oxide
blanc de zinc, flores de zinc, zinc white

Description:
Zinc oxide is a very fine, white or slightly yellowish-white powder. It is odourless. It feels soft when rubbed between two fingers.

Qualities/varieties:
Zinc oxide is widely used as a pigment. Technical qualities such as zinc white may contain various technical additives. In addition, they have other particle size characteristics. A pharmaceutical quality is preferred for dermatological preparations.

Packaging:
Zinc oxide should be stored in airtight containers.

Storage:
Zinc oxide does not require special storage conditions. It has a practically indefinite shelf life.

Hazards/toxicity:
Inhalation of dust particles should be avoided.

Appendix: Water preparation

A.1 Introduction

Water is considered a first necessity of life: living without drinking water is impossible. The World Health Organization has defined the provision of safe drinking water an important millennium goal (MDG 7 target 7.c). Water is widely available although in some areas it may be scarce, of poor quality, or both (1).

Water is also a main ingredient of many preparations in this formulary. More than half of the preparations cannot be produced without water. As it is such an important ingredient, this appendix focusses on how to obtain water of adequate quality for dermatological preparations in a low resource setting.

A.2 Quality requirements for water

Water that is used for dermatological preparations must fulfil certain quality requirements. It must be free from contamination, especially with particulate matter, chemicals and micro-organisms. The same requirements hold for safe drinking water.

Water treatment aims at removing particulate matter and killing micro-organisms. Paragraph A4 gives methods to do this using simple techniques. However, there are no simple, cheap methods to detect or remove chemical contamination. As a general rule, drinking water is only certified as such when harmful chemicals are absent. Therefore, using drinking water for the preparation of dermatologicals is an indirect way to rule out chemical contamination as much as possible.

Drinking water is often contaminated with micro-organisms. It is either contaminated at the source or during storage or transport. We recommend to use drinking water for dermatological preparations and to treat the microbial contamination immediately before use. The first step in any production process involving water is to boil a sufficient amount, as indicated in the preparation monographs in chapter 12.

A.3 Procurement of water

A review of water procurement and treatment is beyond the scope of this formulary. We recommend to consult the relevant local authorities on this issue, and whenever possible to use certified tap water. If drinking water is unavailable, consider the following general rules for water procurement:

- Consult local people. Remember that safe water is of vital importance to them and they usually know where to find water and how safe it is. Respect their rights to drinking water.
- There are ways to filter out particulate matter, and there are simple ways to kill micro-organisms, but there is no simple way to remove chemical contamination. Avoidance of chemical contamination is required.

– If you have to use water from wells make sure they are not contaminated by any human or animal waste. Wells at some distance from habituated areas are likely safer. Avoid wells in industrialized areas or close to waste disposals.
– If you have to use surface water get this as far away from habituated areas as possible. Make sure you do not use surface water near factories or waste disposals, or from places where factories or habituated areas are upstream.

A.4 Water treatment

Water containing particulate matter requires filtering with a suitable filter. If this is unavailable, a clean cloth can be used instead. Subsequently the water must be treated to kill micro-organisms. Appropriate methods are boiling, adding chemical disinfectants, or exposing water to sunlight. The advantages and disadvantages of these methods are summarized in the table. The method of choice depends on the local situation.

Method	***Advantages***	***Disadvantages***
Boiling	* *High certainty that micro-organisms are killed*	* *High cost for fuel* * *Water may get contaminated again upon storage*
Chemical disinfection	* *Does not require fuel* * *Chemical residues may protect from renewed contamination upon storage or transport*	* *Chemical residues can be harmful*
Sunlight	* *Low cost method* * *No residues* * *Environmentally safe*	* *Not effective when the wrong containers are used* * *Effectiveness depends on sunshine and therefore weather* * *Water may get contaminated again upon storage*

A.5 Boiling

Boiling kills all micro-organisms. To achieve this, water must boil at 100 °C for at least one minute. At higher altitudes, i.e., above 4000 meter, the air pressure is significantly lower and water boils at lower temperatures than 100 °C. As a result the boiling is less effective in killing micro-organisms. At altitudes over 4000 meter, boil the water for at least 2 minutes.

A.6 Chemical disinfection of water

Various chemicals are used for water disinfection. Many chemicals are considered unsafe for (human) consumption and are therefore unsuitable for the production of drinking water. Chlorine and iodine are considered safe, although questions were raised about the long-term safety of drinking water treated with iodine. Iodine in low concentrations is considered safe, in contrast to high iodine concentrations which may generate a health risk in the long run (2). Using chlorine to produce drinking water is considered safe.

Numerous preparations are available worldwide for this purpose. Follow the instructions on the packaging. Unfortunately, in low resource areas such products are often in short supply. Possible alternatives are:

- The iodine solution 2% included in this formulary is effective for water treatment. Add 0.4 ml iodine solution 2% for every litre water, stir well, and allow to stand for at least 10 minutes. When the water is visibly contaminated or very cold (below 5 °C) use 0.8 ml iodine solution 2% for every litre water. The latter is a high iodine concentration for safe water production that is suitable for dermatological preparations. It is also suitable to produce emergency drinking water but is unsuitable for long-term water supply. Make sure to use the iodine solution 2% and not the povidone iodine solution (Betadine®) as the latter is unsuitable for this purpose.
- PUR water is a product from Proctor and Gamble aimed at achieving the Millennium Goal of safe water for all. It is used to treat dirty water and is made available at low cost to resource scarce parts of the world (3,4).
- Chlorine disinfectants for household and industrial cleaning purposes are widely available. They often contain other chemicals that are not suitable for human consumption and should therefore not be used for water treatment. Their concentration differs widely. If the presence of other chemicals is ruled out, and the product only contains chlorine, it is suitable to disinfect water in emergency situations. As a general rule, add chlorine and allow the solution to stand for at least 30 minutes. If properly dosed the resulting water has a slight chlorine taste. The proper dose is 2-3 mg free chlorine per litre.

A.7 Sunlight disinfection

UV light from the sun (or artificial sources) kills micro-organisms and has been investigated extensively as a way to disinfect waste water (5). It is considered a suitable technique for the treatment of drinking water, both in the developed world and in regions with limited resources (6). A low tech solar water disinfection (SODIS) has been used now for some decades as a safe and simple technique to provide safe water. The details are found on the website of Climate Lab (www.climatelab.org) (7). The method is as follows:

1. If the water is visibly contaminated it requires filtering first.
2. Fill clear PET (polyethylene terephthalate) bottles of 2 litre or smaller with the water to be treated, leaving at least 2.5 cm free space. Do not use bottles made of other materials.
3. Shake the bottle thoroughly.
4. Put the bottle in direct sunlight, if possible in a warm place, but never behind glass.
5. Leave for 2 days on cloudy days. Hot and sunny weather speeds up the process. In sunny weather 6 hours is enough to get clean water. If the temperature rises to 50 °C and there is full sunlight 1 hour is enough. In very bad weather conditions the process does not work effectively.

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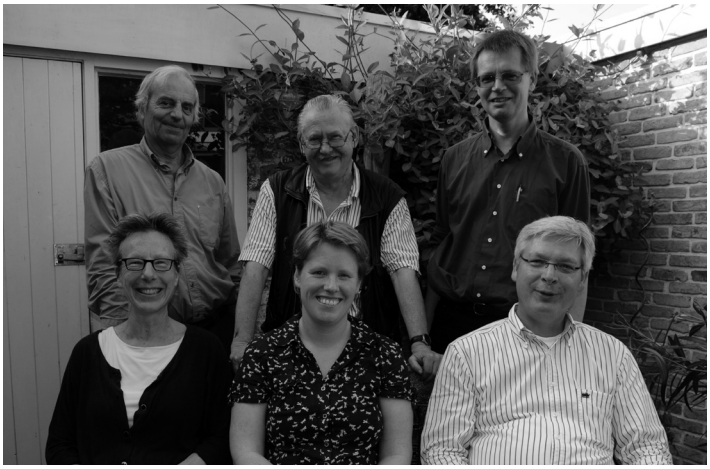

From left to right standing: Vincent Gooskens, Ben Naafs, Peter Bakker. Seated: Nicolien Wieringa, Rachel van der Kaaij, Herman Woerdenbag.

About the authors

Peter Bakker (1961) was trained as a pharmacist. Until recently he worked at Mediq Apotheek Beatrix, Den Helder, the Netherlands, where his main field of interest was strengthening the collaboration between health care professionals in primary care. From 1990 to 1993 he worked as Senior Pharmacy Lecturer at Evelyn Hone College in Lusaka, Zambia.

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Bernard (Ben) Naafs, MD, PhD (1943) was trained as a dermato-venereologist. During the period 1974-1979 he worked in Ethiopia and from 1983-1986 in Zimbabwe. Since 14 years he divides his time between the Netherlands (Antonius Hospital, Emmeloord and Diaconessenhuis, department Steenwijk) and developing countries. Each year he spends 3 months at the Regional Dermatology Training Centre in Moshi, Tanzania, and 3 months at the Instituto Lauro de Souza Lima, Bauru, SP, Brazil.

Rachel M. van der Kaaij, PhD (1976) was trained as a microbiologist. She works as a coordinator at the Science Shop of the University of Groningen, the Netherlands. The Science Shop operates as an intermediary between citizens and non-profit organizations, who experience research questions and issues, and university students and teachers, who conduct research based on these questions.

Nicolien F. Wieringa, PhD (1956) was trained as a pharmacist. Her field of interest is Social Pharmacy. She contributed to various books on social issues of medical and pharmaceutical technologies. Presently, she works as science editor at the Department of Communication of the University Medical Center Groningen, the Netherlands. She was also trained as a professional coach and runs her own coaching practice.

Dermatological Preparations for the Tropics provides practical and background information on the local production of topically applied medicines for the treatment of skin diseases in the least developed countries and regions around the world. It aims to be a reliable source of information to select and to produce dermatologicals: what to prepare for which indication and how to do this? It also gives background information on choices and methods for a better understanding.

The formulary focuses on effective and cheap extemporaneous preparations with sufficient stability, that are suitable for local production and use under tropical conditions. A total of 35 preparations are presented, covering the safe treatment of a broad range of skin diseases.

The book aims to stimulate pharmacists, medical doctors and other health care workers in resource scarce areas to develop local production, dispensing and use of dermatological preparations that meet the specific therapeutic needs, taking into account the given circumstances and limitations.

We hope the book may find its way to the targeted users in a wide range of situations and will prove to be useful in daily medical and pharmaceutical practice.

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