TABU

6 | 2007

RAUHALLISTA JOULUA JA ONNELLISTA UUTTA VUOTTA 2008

GOD JUL OCH GOTT NYTT ÅR 2008

SEASON´S GREETINGS AND BEST WISHES FOR THE NEW YEAR 2008

På svenska | Översättning Mats Försskåhl

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Editorial

European marketing authorisation procedures – scope for further development

Innovative new medicinal products in the European Union are assessed according to the centralised procedure coordinated by the European Medicines Agency, EMEA. Marketing authorisation applications for other medicines are mainly managed in the decentralised and mutual recognition procedures which are based on the mutual collaboration of the national agencies. Nowadays the national marketing authorisation procedure is mainly focused on the maintenance of old authorisations and the evaluation of authorisations for generic medicinal products (future reference member state duties). Rational sharing of work among the national medicines agencies is the aim intended by the EU common procedures. The goal is to avoid overlapping work, in order to have adequate expert resources available for execution of new regulatory duties and to improve the quality of regulation.

Common EU procedures rely on the network of medicines agencies, with EMEA playing the central role. The network model has several advantages in a community like the EU, where the organisation of healthcare, the traditions of pharmacotherapy and the disease epidemiology vary from one member state to another. The future of the network model is dependent on whether the member states wish to contribute to the mutual collaboration by-offering their best expertise for tasks which involve other member states of the EU.

Marketing authorisation applications and applications for variations to the authorisations are fast growing in number. Increased demands on quality assurance and openness, and arbitration procedures associated with disputes between member states make the marketing authorisation processes ever more complicated. Increasing measures are required from the regulatory authorities to improve the availability of medicines, including medicinal products for children and orphan drugs. The extent of scientific and general advice for small- and medium-sized businesses has constantly increased. The implementation of the regulation of developed therapies (gene and cell therapy, tissue engineering) will commence in 2008. This regulation requires the setting up of a new committee within EMEA and, for example, the evaluation of medicinal products while they are still under development.

EU marketing authorisation procedures have generally worked well. Indications of overloading of the system have nevertheless started to emerge in recent years. The problem is also due to causes other than the increased number of applications and regulatory responsibilities. The operation of the medicines regulatory network relies upon the national medicines agencies to take on tasks on behalf of other member states. This principle has not been fully followed, but instead, the mutual responsibilities are shared by too few medicines agencies.

A lack of resources and expertise at EU level may hinder a state from operating as a rapporteur or as a reference member state in the centralised, decentralised or mutual recognition procedures. The lack of contributions may also be explained by the heavy responsibilities involved in the procedures which the reference or rapporteur state will have to accept. The heavy assessment process in respect of the centralised procedure can be justified by the extent of evaluation, by the innovativeness of the drugs under evaluation, and by the genuine intention to listen carefully to the applicant and the experts. The decentralised and mutual recognition procedures involve national interests and, at worst, mutual lack of trust among the authorities. Common decisions sometimes require harmonisation of national regulatory principles and even of treatment practices, while the member states generally show great reluctance to accept this.

We have a situation at present, where agencies that are active in reference member state duties have one after the other been forced to accept that they are no longer coping with the processing, within the due period, of the applications for marketing authorisations submitted to them. NAM has also been immersed in a severe backlog of applications. Analysis of the situation is followed by a conclusion that the operational procedures should be changed by streamlining, prioritising and automating the assessment and administration of applications. A paper in this issue of TABU describes the status of marketing authorisation procedures and a strategy for reinstating a marketing authorisation application procedure which is able to respect the due dates without jeopardising the safety of medicines or NAM's strategic aims.

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Recent developments in pharmaceutical policy

Several reforms have been made in the Finnish pharmaceutical service in recent years, focusing on the management of pharmaceutical costs in particular. Concern for the rise in pharmaceutical costs has increased with the introduction of expensive new drugs onto the market and an ageing population. In the Government Programme (1) of Prime Minister Matti Vanhanen's second Cabinet, the definitions of pharmaceutical policy emphasise cost-effectiveness and restraining the rising costs but also focus on safe pharmacotherapy, securing extensive pharmaceutical service and introducing a just ceiling system with regard to client charges in social and health care services (1).

Restraints on drug costs

In 2005, pharmaceutical costs represented 16,3% of the total healthcare expenditure (2), and in the first years after 2000, real annual growth in costs was between 4% and 8%. Pharmaceutical policy measures taken in recent years have nevertheless yielded at least short-term results in cutting pharmaceutical costs. In the year 2006, the wholesale value of outpatient drugs decreased for the first time for decades. This resulted from the 5% cut, implemented at the beginning of 2006, in wholesale prices for refunded drugs, as well as from drug price competition which was partly influenced by increased generic substitution in 2006. The strategy of the Ministry of Social Affairs and Health (MSAH) (3) has even set the annual real growth limit for refunded drug costs at 5% for the years 2008 to 2011.

A working group focusing on a reference price system for drugs investigated preliminarily two main models and their effectiveness in the medicine reimbursement costs. In the generic model, the preparations are grouped on the basis of the active substance, whereas in the therapeutic model they are grouped according to their therapeutic equivalence. The working group considered it possible to implement the generic model in a few years' time (4). Switching to a reference price system would follow the general European trend and be a consistent continuation of the generic substitution system adopted in 2003.

Improved cost-effectiveness

The main pharmaceutical objective within the strategy of the MSAH (3) consists of increasing the cost-effectiveness of pharmaceutical services, for example by creating incentives to promote rational prescribing practices. Cost-effectiveness could also be enhanced by increasing the market share of generic products, which at present is smaller in Finland than in many other European countries (5).

The present government aims to reform the drug reimbursement system in a cost-containing manner, but the importance of cost-effectiveness will also be recognised, particularly with regard to new medicines (1). Assessing cost-effectiveness would nevertheless require an increased level of capacity, especially in health economics (5). Pricing and reimbursement policy and assessment of the relative effectiveness of medicines are at present central themes also in the European Union's pharmaceuticals policy (6).

The Pharmaceuticals Pricing Board decided in 2006 to restrict reimbursement of two of the most expensive anti-cholesterol agents. The restriction contained a novel requirement according to which the patient must, under certain conditions, be switched to another active substance of the same drug group. The motivation for the decision was the marginal additional benefit obtained from the most expensive statins compared to the extra costs involved (7). In 2007 the Pricing Board, exercising for the first time the right granted by the Sickness Insurance Act reform, discontinued reimbursability of a drug still covered by a product patent in several other EU countries (8).

Other recent themes

Problems associated with responsibility for covering the costs of medicines may result in inappropriate decisions shifting responsibility for care and costs to another funding channel (3). The complicated system of public funding of pharmacotherapy services should undergo a total reform, so that irrespective of the distribution area, sickness insurance should compensate for all drugs covered by the reimbursement system, and the municipalities would continue to cover the costs for all non-refundable outpatient drugs (9).

The reform of the Sickness Insurance Act that came into force on 1.1.2006 fulfilled several of the objectives of the pharmaceutical policy. The drug refund system was largely revised. A reform of the Medicines Act that came into force on 1.2.2006 prevented pharmaceutical companies and pharmacies from establishing rebate agreements with pharmacies. In 2006, licensed sales of over-the-counter nicotine replacement products were allowed outside pharmacies. A three-year trial of selectively reimbursing the costs of dose dispensing service was launched by the MSAH in 2005 and can be expected to continue. Adoption of electronic prescriptions is also expected to improve individual patients' medication management. The Act on Electronic Prescriptions came into force on 1.4.2007, but there will be a four-year transitional period before the system is fully implemented.

Pharmaceutical policy in the present term of government

Concern for rising pharmaceutical costs is reflected in the policy definitions of the present government (1). The government is committed to curbing the rising costs, and some type of reference price system is likely to be introduced. In addition to costs, the government platform will also tackle cost-effectiveness, which reflects the shift of attention from drug prices to the functionality of the entire treatment chain. With developed pharmacotherapies it is possible to achieve cost savings, for example, as a result of a long-term reduction in the need for institutionalised care and improved employability.

A government platform that highlights the promotion of safe pharmacotherapy and the safeguarding of extensive pharmaceutical services can be considered a significant statement of principle. The pharmaceutical services will be secured by developing the system of subsidiary pharmacies and licensed medicine chests (10).

In the present term of government the relevance of the Pharmaceuticals Pricing Board as a pharmaceutical policy operator is greater than before. The functioning of the Pricing Board has nevertheless been criticised for lack of transparency in its decision-making procedures. It has even been suggested that the pricing and reimbursement decisions be separated from the assessment of therapeutic value of a drug by establishing an independent agency for the latter (5). Improved definitions of criteria and more detailed decisions from the Board would increase the openness and transparency of the process (5). Potential for increased coordination of expertise and assessment of cost-effectiveness of drugs are indeed to be reviewed in the present term of government (11).

The aims defined in the present government platform (1) and the strategy of the MSAH (3) are in line with the key objectives of the document Pharmaceutical Policy 2010 (12), in particular as regards appropriate drug use, reasonable drug costs, safe pharmacotherapy, regional availability of pharmaceuticals and promotion of Finnish pharmaceutical research. Current issues of interest also include problems of the pharmaceutical services mentioned in Pharmaceutical Policy 2010, such as rapidly rising costs, a two-channelled public funding system, and possible delays in introduction of new drugs onto or their total absence from the Finnish market.

The Finnish pharmaceutical policy can be considered consistent as far as major definitions of policy are concerned, but its consistency has in recent years been reduced by measures aimed at cost restriction which have often been introduced quickly. For a successful pharmaceutical policy, perseverance and improved predictability are required. The better the pharmaceutical sector is able to predict the direction of change, the easier it will be to prepare for reforms and ensure uninterrupted pharmaceutical services.

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Terbinafine – a matter of taste

Terbinafine, topically or orally used, is an effective drug in the treatment of dermatophytosis. It is a fungicide, but not completely free of harmful adverse effects. Most of the harmful effects of terbinafine were already known when it was registered by the British for the first time in 1991.

A course of treatment with terbinafine, even one lasting for months, does not cause a problem in 90 out of 100 patients. Stomach complaints, taste disturbances or drug-induced rash may, however, occur in the remaining 10. Other adverse drug reactions are rare, and severe ones are very rare.

Stomach complaints

There is no stomach complaint typical of terbinafine alone. The symptoms may include pain, diarrhoea, and/or flatulence. It would be a good idea to take terbinafine with food, even though this is not an official recommendation. The absorption of the drug is slightly improved when taken with food (below 20% increase in the AUC), and the risk of stomach complaints is probably reduced.

Disappearance of the sense of taste

A change in or loss of the sense of taste during a course of terbinafine therapy is possible, but it is almost without exception transient; it resolves within 1 to 2 months. A disturbance in the sense of taste is often associated with the long-term treatment of onychomycosis, but it is also possible with only a two-week course of treatment.

I have advised my patients to complete the whole course of treatment even if their sense of taste is lost; withdrawal of the course would jeopardise the result of the treatment. During my 15 years of experience in prescribing terbinafine, none of my patients so far has reported a permanent taste disorder.

There are isolated reports of impairment of the sense of smell during a course of treatment – often in association with a disturbance of the sense of taste.

Skin reactions

It is well known that oral terbinafine can cause skin reactions. Their morphology is usually similar to that of urticaria, exanthema and *Erythema multiforme*. Through the years, AGEP (*Acute Generalized Exanthematous Pustulosis*) has also become to be included among these, as a rare reaction.

Statistically the risk of developing the condition of *Erythema multiforme* major, i.e. the Stevens-Johnson syndrome is 1:350,000 and that of Lyell's syndrome (*Toxic epidermal necrolysis*) even smaller.

If the patient reports having had a rash during a course of terbinafine therapy, the course should be discontinued immediately and not reinstated until the type of the skin symptom is assessed by actually meeting the patient face to face.

On the one hand, the effectiveness of medication with terbinafine is not being impaired through the temporary discontinuation of the medication, and on the other, not all rashes during medication are caused by the drug itself. To try to 'identify' the skin symptom by telephone is also quackery in such a case.

Rare severe adverse reactions

Even though terbinafine can cause severe disturbances of the blood count and liver function, these are rare enough for no laboratory monitoring to be necessary during the course of treatment. Earlier liver problems should be taken into account and possible clinical symptoms should be noted.

Interactions

Even though terbinafine is nevertheless not entirely free of the risk of interactions, it is harmless in comparison with the azole drugs. The concentration of drugs using the CYP2D6 system in their metabolism may (mainly based on the information gained through *in vitro* studies) increase during terbinafine therapy, but I have not encountered any problems with patients receiving for example, beta-blockers. If the patient uses drugs metabolised by CYP-2D6 with a narrow therapeutic window, it is recommended that the details of interactions contained in the SPC be closely checked.

Adverse reactions in Finland?

From the year 2000 to the end of April 2007 a total of 123 reports concerning terbinafine were received by the *National Adverse*

Drug Reaction database in Finland. During the same period, daily doses (250 mg) of oral terbinafine were sold in Finland amounting to 17.8 million. On the assumption that all adverse reactions have been reported, the intake of one tablet is consequently associated with an adverse reaction risk of about 0.7 per thousand. As the majority of the sales was principally of packets of 28 tablets, the most common therapeutic indication is probably onychomycosis, the recommended length of treatment with terbinafine is 3 months = 3 x 28 tablets. Based on the information available on this register the course of treatment for dermatophytes therefore appears to be associated with a less than 0.1% risk of adverse reactions.

Previous clinical studies actually show the real risk of adverse reactions to be about 10%. The purpose of an adverse drug reaction register is, in fact, detecting unexpected, serious and less common reactions. Since terbinafine actually was in use in Finland for about ten years prior to the reporting period mentioned, stomach complaints and disturbances in the sense of taste usually fall below the reporting threshold.

One would imagine that along with the patent for terbinafine having become outdated, the dropped price would have increased both its use and the adverse reactions. However, the total sales of the drug remain unchanged. That's as it should be.

The true effectiveness of the treatment?

I promise to patients suffering from dermatophyte infection of the skin that the disease is definitely resolved with terbinafine – at least after an oral intake, if topical treatment is not sufficient in that specific case. The same can be promised about finger nails, but the prognosis for onychomycosis of toe nails, which grow three times slower, can be judged by tossing a coin. The average chance of a full recovery from toenail onychomycosis is tantamount to 'heads or tails'.

The usual dermatophytes in between the 4th and 5th toes ought not to be treated with oral terbinafine; topical treatment will cure them. If not, dermatophyte infection is the incorrect diagnosis or there is something else also wrong with the skin as well. If dermatophytes are present on the sole of the foot, they will not resolve with topical antifungal – but they will be alleviated – and will thereafter spread to the nails, too.

What about the treatment alternatives?

In principle, topical treatment alone could of course be considered for both the dermatophytes of the skin and the nails. However, topical treatment for the nails is only effective in the most mild cases of distal infections. Nor should the strong, 28% tioconazole solution be used in their treatment; it probably causes more drug allergies than it cures. Amorolfine lacquer is at least less harmful.

A case of its own is represented by a south-west Finnish 'antifungal' preparation, which is not burdened by research evidence or the drug advertising rules that medicinal products are governed by.

Should a diagnosed disease always be treated with drugs?

Should a doctor actively offer a drug for the treatment of onychomycosis of which he has made a diagnosis 'in passing'. Will a spreading outbreak of onychomycosis occur if it is left untreated?

When even by trying hard and with optimal growing conditions for the fungi as many as 50% of the cultivation samples are incorrect negatives, I find it hard to believe that dermatophytes of the nail would jump from the nail to one's own skin, let alone that of close relatives.

At least as far as the elderly on a multitude of drug therapies are concerned, it is advisable to use common sense when considering long courses of treatment for onychomycosis.

How can the adverse reactions caused by terbinafine be reduced?

According to practical experience, oral antifungals are prescribed with inadequate evidence for the role of dermatophyte in the clinical symptoms. If the diagnosis of dermatophytosis (infection caused by a dermatophyte) is unclear, a therapeutic trial with an oral antifungal should not be performed. Unnecessary treatment exposes the patient to unnecessary risk for adverse drug reactions. In the case of a serious adverse drug reaction the situation of the doctor is also lamentable if there is no real reason for the treatment.

We all make wrong diagnoses. In dermatophytosis they can be reduced by taking fungal samples. If treatment is urgently required – which is seldom the case in a dermatophytosis – direct microscopy of the specimen may provide an additional clue to the clinical assessment, sometimes even evidence enough for the start of the therapy. It is nevertheless only a fungal culture that confirms the diagnosis and the species of the fungus, which especially in scalp infections has an effect at least on the length of the medical treatment.

Fungal specimen are also associated with their own sources of errors. The specimen may be taken from a non-representative site or may be inadequate. The sample collector should be well acquainted with her job.

Repeated minimal nail injury, caused by unfitting shoes, may cause onycholysis. This must not be interpreted and treated as onychomycosis.

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Articaine-containing local anaesthetics and sensory disturbances

Local anaesthesia in dental procedures is estimated to be associated with a 0.15%–0.54% risk of transient sensory losses and changes. Permanent sensory losses occur significantly less frequently, in 0.0001%–0.01% of local anaesthetic procedures. In comparison with other anaesthetics, more frequent local nerve injuries are suspected to have been caused by articaine (1).

A sensory loss (*hypoaesthesia*) is manifested as impaired tactile sense, whereas sensory changes (*paraesthesia*) are manifested as tactile hallucinations such as burning or stinging. Paraesthesia may also be associated with hyperaesthesia, increased sensibility or dysaesthesia, changed sensory sensitivity. In addition to adverse reactions caused by articaine-containing local anaesthetics in association with dental procedures published in the literature, we will discuss in this article also those reported to the adverse drug reaction register of NAM (National Agency for Medicines).

Articaine has been in use in Finland for over 20 years. Local anaesthetics containing articaine are available on the market under three different trade names: Septocaine, Ultracain D-Suprarenin and Ubistesin. These products contain 40 mg/ml articaine and 5 microg/ml or 10 microg/ml adrenaline. Adrenaline is used because of its vasoconstrictive effect, i.e. it contracts the blood vessels. Vasoconstriction slows down the absorption of articaine resulting in a higher concentration at the injection site and prolongation of the duration of effect.

Products containing articaine can be used for both infiltration and nerve block anaesthesia. In infiltration anaesthesia the anaesthetic agent is injected into the area of the procedure, and in nerve block anaesthesia adjacent to a nerve supplying the area of the procedure. For example, anaesthesia is achieved in the teeth of the lower jaw by nerve block anaesthesia of the inferior alveolar nerve up to the midline of the lower jaw on the side which is to be anaesthetized. Generally the lingual nerve is also anaesthetized due to its close proximity. The amount usually used in local anaesthesia, e.g. in association with tooth removal, is one ampoule (1.7 ml) of an articaine preparation, which contains 68 mg of articaine. The effect starts within a couple of minutes and usually lasts for about 2 hours following infiltration anaesthesia and up to 4 hours following nerve block anaesthesia.

Once introduced onto the market, articaine achieved popularity because it contained preservaties that were less likely to cause allergy than those included in other local anaesthetic agents in use at the time. A similar difference does not exist anymore for example, with lidocaine. In principle, articaine is a safer local anaesthetic than lidocaine due to its shorter half-life. In comparison with other amide-containing local anaesthetics, articaine has a broader therapeutic spectrum which consequently permits the use of higher concentrations (articaine 4% vs. lidocaine 2%), resulting in a smaller volume of injection of the local anaesthetic being administered.

Consumption of dental local anaesthetics

In 2006 the consumption of products containing articaine totalled 2,193,150 cylinder ampoules (the volume of one ampoule being 1.7 ml) and sales have been constantly increasing since the year 2000 (Fig.).

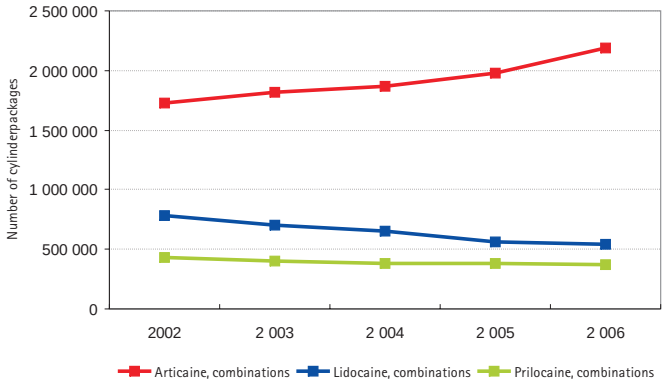

Fig. The sale of dental local anaesthetics in the form of cylinder ampoules in 2002–2006.

Reports of adverse reactions

A total of 84 adverse reactions caused by dental local anaesthetics were reported to the National Agency for Medicines up until the end of October 2007. Adverse drug reaction reports received on products containing articaine totalled 52, and they included 82 different reactions (Table 1). The most frequently reported symptoms concerned sensory losses and changes in the face, lips or tongue (12 reports, Table 2). Not a single report was received concerning these symptoms in association with other dental local anaesthetics.

Discussion

Haas and Lennon reported in 1995 (2), that there were Canadian reports of a higher risk than expected of sensory changes involved in local mandibular (lower jaw) anaesthesia using articaine. A researcher (3) who had reassessed these reports claimed that the risk with articaine would be as much as 20 times higher than that with lidocaine. Malamed et al. (4) compared the adverse reactions that had occurred in 1,325 patients with local infiltration or nerve block anaesthesia using either 4% articaine or 2% lidocaine and claimed that the frequency of sensory losses and changes (4–8 days after local anaesthesia) was 1% with both the local anaesthetics used. In this study the symptoms were reversible.

The Danish drug authorities reviewed the spontaneous reports of sensory losses associated with the use of articaine and concluded that there is no proof so far of any greater neurotoxicity being associated with articaine in comparison with other local anaesthetics (5). Hillerup et al. (1) carried out a review of 52 patients, who were afflicted with nerve damage in association with a local mandibular anaesthetic. These patients experienced lingual nerve damages more frequently and with more complicated symptoms than inferior alveolar nerve damage. In this patient material 4% articaine caused 54% of the nerve damages, but the researchers did not make a relative comparison between the extent of the damage and the number of local anaesthetics given.

Based on the data received from the studies so far it is impossible to produce an accurate estimate of the extent of risk of sensory losses or changes involved with the use of articaine. However, it appears to be an uncommon adverse reaction and there is no certainty that the risk with articaine-containing products would be higher than with other local anaesthetics.

There have also been reports of sensory loss or of changes associated with the use of articaine in Finland. The total number of reports is 12. Some patients exhibited symptoms up to 6 months after the administration of the local anaesthesia. The symptoms can be hard to handle, including for example speech difficulties or alterations in the sense of taste as a result of a sensory loss, making life therefore difficult. There was a likelihood in at least four cases that the adverse reactions were not associated with articaine contained in the local anaesthetic (Table 2). The senses of feeling focussed on the eye and the observations made at the opposite side of the face indicate that the anaesthetic agent has been transmitted to an incorrect area. The unwanted reactions focussing in the area of the eye as such are possible for example in the local anaesthesia of an upper canine tooth. Anaesthesia of the ocular motor nerve can affect the extraocular muscles, the movement of the upper eyelid (manifested especially as a difficulty of keeping the eye open) and contraction of the pupil. An accelerated pulse and malaise are known sympathetic effects of adrenaline when the local anaesthetic enters the blood circulation. Fear of treatment may also cause or aggravate similar symptoms in patients.

Conclusions cannot be drawn based on the adverse drug reaction reports received by NAM in respect to the incidence of these reactions, because not all adverse reactions are reported – especially not the transient types, which the majority of the sensory losses caused by local anaesthetics are. It is recommended that the healthcare personnel should bear in mind the meaning of the reports of adverse reactions while information is being compiled relating to the adverse reactions, as this information is helpful in making important observations about the safety of use of medicines at the population level.

Table 1. Adverse reactions caused by local anaesthetic products containing articaine and adrenaline reported to the ADR register of NAM.

Adverse reaction	*Number of reports*
Sensory losses or changes in the face, lips or the tongue	*13*
Nausea or vomiting	*11*
Urticaria or other rash	*9*
Anaphylaxis	*8*
Palpitations	*8*
Oedema of the face, mouth or the pharynx	*6*
Somnolence, fatigue or hypotonia	*4*
Injection site reaction	*4*
Dizziness	*4*
Syncope	*4*
Dyspnoea	*3*
Convulsions	*3*
Other	*5*

Table 2. Reports which included a mention of a sensory loss or change in association with the use of a local anaesthetic containing articaine and adrenaline.

	Patient	Description of the adverse reaction
1)	A 24-year-old female	The local anaesthetic used was Ultracain D-Suprarenin (no information about the dose or the method of administration). The patient had an odd feeling in the eye, difficulties in keeping the eye open and a glassy pupil on the side other than that injected with the local anaesthetic. The adverse reaction was possibly due to the anaesthetic technique used or to anatomical variations, and in consequence the role of the local anaesthetic in causing the adverse reaction is unclear.
2)	A 3-year-old boy	1.7 ml injection of Ubistesin was followed by a severe burning pain in the tongue and the lip on the left side, i.e. anaesthesia was not achieved in the intended area. The pain was relieved after a while at home.
3)	A 58-year-old male	Local infiltration anaesthesia due to root treatment of d35 (1 ampoule of Ultracain D-Suprarenin). Half a year later, sensory loss remained in the left lower jaw.
4)	A 29-year-old female	Local infiltration anaesthesia in the mucous membrane at d17 (Ubistesin 1.7 ml). After about 10 minutes, a feeling of anaesthesia in a wider area than expected developed together with malaise and palpitations. The symp toms were probably caused by adrenaline.
5)	A 24-year-old female	Local infiltration anaesthesia in the mucous membranes at d15 (Ubistesin 1.7 ml). A feeling of anaesthesia in a wide area, malaise, palpitations and light-headedness followed. The symptoms were probably caused by adrenaline.
6)	A 26-year-old female	Immediately following local nerve block anaesthesia in the lower jaw (Ubistesin 1.7 ml), there was contraction of the surface vessels of the left side of the face and anaesthesia of the upper eyelid. The symptoms disappeared within a couple of minutes, the probable cause of them being adrenaline.
7)	A 52-year-old female	Local nerve block anaesthesia in the left lower jaw (Ultracain D-Suprarenin 1.7 ml). The tongue was still anaesthetized and stiff 2.5 months later.
8)	A 47-year-old male	A local anaesthetic (Ultracain D-Suprarenin 3.4 ml) was given due to root treatment of d36, which was followed by sensory loss in the lip and cheek on the left side. Gradually the sense of feeling in the cheek became hypersensitive, and the feeling returned to normal a couple of months after the administration of the local anaesthetic.
9)	A 34-year-old female	The total Ubistesin used was less than 3 x 1.7 ml for local infiltration anaesthesia due to root treatment of d27. A feeling of anaesthesia in the cheek continued for 4 weeks following treatment. A couple of months later a small area in the cheek developed hypersensitivity to touching. The sense of feeling later returned to normal.
10)	A 46-year-old female	The patient had undergone surgery for the removal of d37, the local anaesthetic used was Ubistesin 1.7 ml and there was no special sense of feeling during local anaesthesia. Following the procedure, however, the lip and the tongue remained anaesthetized, including a feeling of odd stinging and itching, but no aching. The tongue has no sense of taste on the left side, and the tongue gets tired while the patient is talking, making talking laborious.
11)	A 31-year-old female	Local nerve block anaesthesia (Ubistesin 1.7 ml) due to filling of d46. Within the next few days following anaesthesia the entire right side of the tongue still felt anaesthetized, and three weeks later the sense of taste at the back of the right side of the tongue was still absent.
12)	A 40-year-old female	Local nerve block anaesthesia with Ubistesin 1.7 ml due to surgery of d36. The left side of the face was anaesthetized to the extent that the left eye would not close at all. The duration of effect of the local anaesthetic agent was 5-6 hours. The tactile sensitivity in the left cheek thereafter was less than that in the right cheek.

The Finnish material and international studies suggesting that articaine would increase the risk of sensory losses or changes at most give guidance, and there is no reliable evidence of the neurotoxicity of articaine. It is suggested, nevertheless, that at the higher concentration articaine-containing products can cause a higher risk of nerve damage (1). Consequently, in the use of articaine-containing and other local dental anaesthetics effort should be made to keep the injected dose of the anaesthetic as low as possible by using careful anaesthetic techniques.

See literature on page 26.

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Further development of the management of marketing authorisation issues

NAM's marketing authorisation department was restructured in 2003 in order to streamline marketing authorisation processes and promote pursuit of the strategic aims of the NAM. Thanks to the restructuring, considerable progress was made in terms of achieving these aims. It became gradually clear, nevertheless, that old working methods still prevailed while new tasks were adopted. Consequently, the handling of processes was not sufficiently improved in order to achieve clearing the ever-growing backlog of applications.

Applications since 2000

Finland was flooded with national marketing authorisation applications for generic medicinal products, especially in the years after 2000. The biggest waves of applications came in the years 2004 to 2005. Marketing authorisation holders of these products regularly request that Finland (NAM) becomes the European reference member state for their products. A statement was issued by NAM on its website in 2005 in which the backlog of applications was openly admitted and applicants were asked to explore other routes, particularly where their product was not actually intended for the Finnish market. This act reduced the annual number of national marketing authorisation applications (Fig. 1).

At the same time, the total number of other marketing authorisation applications, applications for variations and notifications has continued to grow rapidly (Fig. 2).

Goals of the marketing authorisation department

The processing of applications is governed, among other things, by dead lines stipulated in the Medicines Act and Decree. NAM is expected to be an active player in the EU Regulatory Network for medicinal products, to promote healthy pharmaceutical markets, to facilitate electronic submissions, and improve the availability of independent drug information. In light of the present work situation and available resources, it is, however, very challenging to achieve this target.

Strategic means

Nationally, it is very important to ensure compliance with the stipulations of the Medicines Act, to ensure the maintenance of expertise in drug regulation and drug development in Finland, and to promote Finnish national interests in the EU. The marketing authorisations department aims to facilitating work sharing among national competent authorities. There is a desire to put more trust in the work of other national agencies, and to comply with mutually agreed guidelines.

The processing of marketing authorisation applications is simplified through the avoidance of repeated requests for additional information in the national procedures and of rounds of for comments and responses in the mutual recognition and decen-

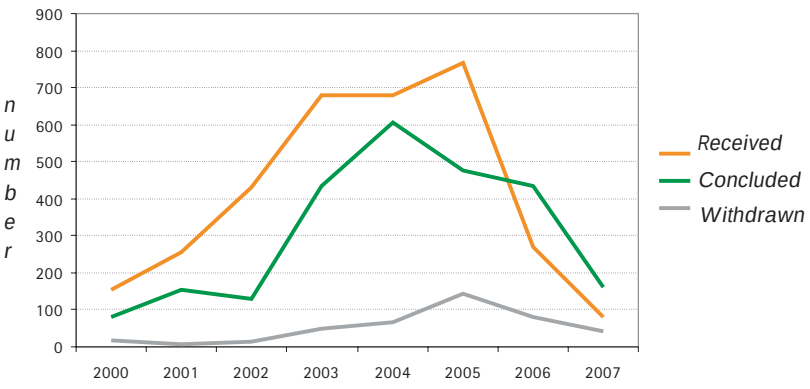

Fig 1. Received, withdrawn and concluded national marketing authorisation applications in 2000–2007. Figures for 2007 refer to January–October.

tralised procedures. The praxis that the authorities will check everything and will finally fix the deficiencies must be abandoned. Optimum use of expert resources is achieved by prioritising tasks in respect of drug safety.

Electronic submission and management of regulatory information, electronic submission of marketing authorisation applications in particular will be introduced. This will improve the running of operations and the associated monitoring of work flow, and will also release resources from several tasks which until now have been carried out manually. The aim is to adopt a service-based operational model for marketing authorisation issues where the processes and customer relationships form the key guiding factors. Information on the NAM website relating to the marketing authorisation system will be expanded and updated.

NAM wants to do its part to ensure the availability of generic drugs not only nationally, but also throughout the European Union area, and thereby to promote the fair sharing of work as well as mutual trust among member states. This is the only way of solving the work overload situation with which all member states are struggling.

As part of the centralised marketing authorisation procedure, the European Medicines Agency (EMEA) grants evaluation (reporting) duties to national agencies in accordance with their expertise and experience. NAM works actively within its area of specialisation in order to maintain its level of competitiveness.

In the regulatory work, we need to focus increasingly on the availability of medicinal products, and to support drug development (e.g. scientific advice). As Finland is a small market area, we often encounter problems in availability of important medicinal products, including veterinary medicinal products. Safeguarding the disease-free state and public health issues associated with animals in commercial production are key issues to consider in the field of veterinary medicinal products.

The job descriptions of personnel in the marketing authorisation department are being upgraded to meet the future challenges. The need to develop competence according to the needs of the organisation from the individual starting points of each member of the personnel will be given ever more emphasis in future. The multidisciplinary approach to the evaluation work is promoted.

Organisational and operational changes

In 2007, five sections of the marketing authorisation department were reorganised to leave just three, namely the Sections for Innovative, Generic and Veterinary Medicines. This reorganisation improved the effectiveness of management operations by making a distinction between managerial and expert roles. The tasks of the Sections for Innovative and Generic Medicines were expanded. The department includes a management group with the task of synchronisation of the work in the three sections, promoting scientific expertise for centralised EU processes, management of development projects and legal/administrative policy making.

The Section for Innovative Medicines processes all applications relating to brand-name drugs. The work of all 35 employees in the section focuses mainly on the management of rapporteur/co-rapporteur duties as part of the centralised procedure as well as certain national, mutual recognition and de-centralised marketing authorisation applications. The section is also responsible for national and EMEA scientific advise and for the evaluation of herbal medicinal products. Experts of this section are also involved in the work of the new paediatric committee which was set up and commenced operation in July 2007. A degree relating to advanced therapies, which is set to become effective as of next year, will also create new responsibilities for the section.

Since the reorganisation, the section has focused on stabilising operations and clearing the back-

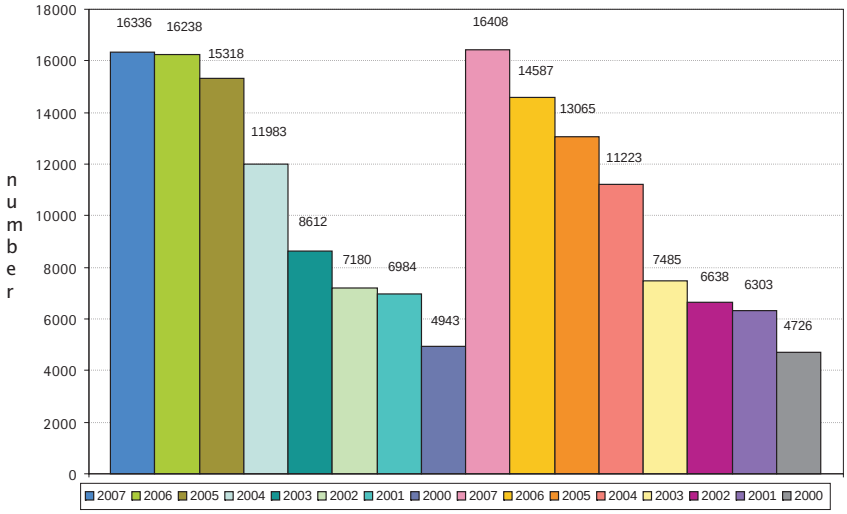

Fig 2. Received and concluded applications/notifications – development in the reference period of 2000 to 2007. Until 2006 the number of concluded processes remained smaller compared with that of received applications and notifications.

log of national applications. Collaboration with the generic drugs section has been intensified and both sections have set their sites on achieving effective, standardised processes.

The Section for Generic Medicines was expanded at the beginning of 2007 to include parallel imports and distribution, as well as some of the joint processes and development tasks of the marketing authorisation department. The section has approximately 40 employees. All sorts of generic drugs are now managed in the same section, and operations supporting common department issues are best suited to this section. During 2007 the generic drugs section has also stabilised its operations. There are now fewer changes in personnel and the section is well on its way to clearing the backlog.

The structure of **the Section for Veterinary Medicines** remains unchanged. This section can be best described as the NAM in miniature, because its operations include several functions which with regard to human medicines have been divided into different departments. Besides marketing authorisation applications, the section for veterinary medicines also deals with notifications of clinical trials on veterinary medicinal products, special licences for the release of a veterinary medicinal products and pharmacoviglilance. The section takes part in EU collaboration in the European Medicines Agency. Regulation of veterinary medicines is linked to significant national interests relating to public health and the disease-free status of the production animals. There is currently a delay in the processing of applications for renewals and variations. The section is relieving its own backlog by prioritising the marketing authorisation application process, which is carried out in a straightforward fashion, avoiding repeat requests for additional reports.

Monitoring of the processes

By its nature, NAM's marketing authorisation application process produces an abundance of data and statistics, but to interpret these in such a way as to monitor processes meaningfully has proven difficult for many reasons: the process contains several phases and a number of operators, with bottlenecks developing at different stages at different times. Furthermore, the workload of different expert groups cannot be measured using the same standards. A process tracking system has been developed to solve these problems. Possibilities for monitoring personal performance and workload have also been improved. New, easy-to-use monitoring instruments will be introduced by the end of the year.

In 2005, NAM introduced a system for monitoring the time spent for various tasks by its personnel. The system also provides information regarding the costs of core operations. Managers at different levels use these data for monitoring and ensuring proper targeting of resources. The data obtained from this system have made it possible to assess the human resources needed for the project for cutting queues.

Regulatory guidance

Scientific evaluation of medicinal products is conducted according to NAM's standard operation procedures. The guidelines start from the premise that the aim should be for Finland to recognise marketing authorisations evaluated by a reference member state, and that only in exceptional cases should Finland object to the scientific evaluation of a medicinal product by a reference member state in the marketing authorisation process (*only in case of a justified potential serious risk to human or animal health or to the environment*).

Furthermore, standard operational procedures aim to bring clarity to the interactions between the applicant and NAM. This is achieved by accelerating the inquiry and hearing proceedings stipulated in administrative legislation so that hearing proceedings can start immediately, if the application for marketing authorisation is immature. At the stage of the marketing authorisation process where the applicant has the opportunity to reply to an inquiry by NAM, the intention is that one round should be sufficient for the decision making. If this response is not adequate, the application is to be rejected on grounds of immaturity.

The revised Medicines Directive includes an article called the Sunset Clause, which is implemented in subparagraph 3, paragraph 1 of Section 29 of the Medicines Act (395/87). According to this article, the marketing authorisation and registration will become invalid if the marketing authorisation holders have not introduced the product onto the market within 3 years of the marketing authorisation or registration being granted, or if the presence of the product on the market has been continuously interrupted for three years. Amended Section 29 of the Medicines Act (395/87) came into force on 7.11.2005. The legal implications of the statute on marketing authorisations of medicinal products will become effective as of 7.11.2008. According to the view adopted by NAM, this section of the legislation will not be applicable to products which have been granted marketing authorisation via the centralised procedure, nor will it be applicable to medicinal products with parallel import licences.

A statement prepared in response to the Sunset Clause is published on NAM's website. The bulletin on the website includes additional guidance for marketing authorisation holders regarding interpretation of the

various concepts, time schedules, methods of operation, etc.

Electronic management of regulatory information

The chief project in NAM's electronic management of regulatory information is the change to electronic processing of marketing authorisations. The main aim of the project for the marketing authorisation department is to make operations more effective and to facilitate handling through the simplification and acceleration of the various stages of the processes. Tendering for delivery of the electronic management system is underway, and the project is expected to be up and running at the beginning of 2008. Collaboration with stakeholder groups forms an important part of the scheme.

Special project for clearing the backlog of applications

At the end of February 2007, NAM set up a 2-year project called 'JoPo' to clear the backlogs of applications. The project got off to a good start. By the end of November, over 50% of the applications designated as part of the project had already been processed. The progress of the project is monitored very closely.

Effects of the new regulatory policy

The aim of the new policy and associated measures is to prioritise and improve the scientific evaluation as well as coordination and processing of marketing authorisation applications. The implications that this will have to marketing authorisation applicants and holders are reflected, for example, in the reinforcement of the regulatory i.e. supervisory role of the authority. A good application will pass through the process quickly, while a bad one will not pass through at all. Primary responsibility for the quality and user-friendliness of the SPCs and package leaflets lies with the marketing authorisation applicants and holders. Pharmaceutical companies must realise that the authorities are not able to take on the burden of editing poor-quality documents to the stage where they can be approved. This work must be carried out by the pharmaceutical companies themselves, with the only alternative being rejection of the applications. Prescribers and users of medicinal products should become accustomed to the fact that the product information for medicinal products, e.g. generic products, assessed by other competent authorities may in some cases differ from that of the local innovator medicinal product which was originally approved in Finland. Switching to electronic submissions requires that applicants start using the eCTD format.

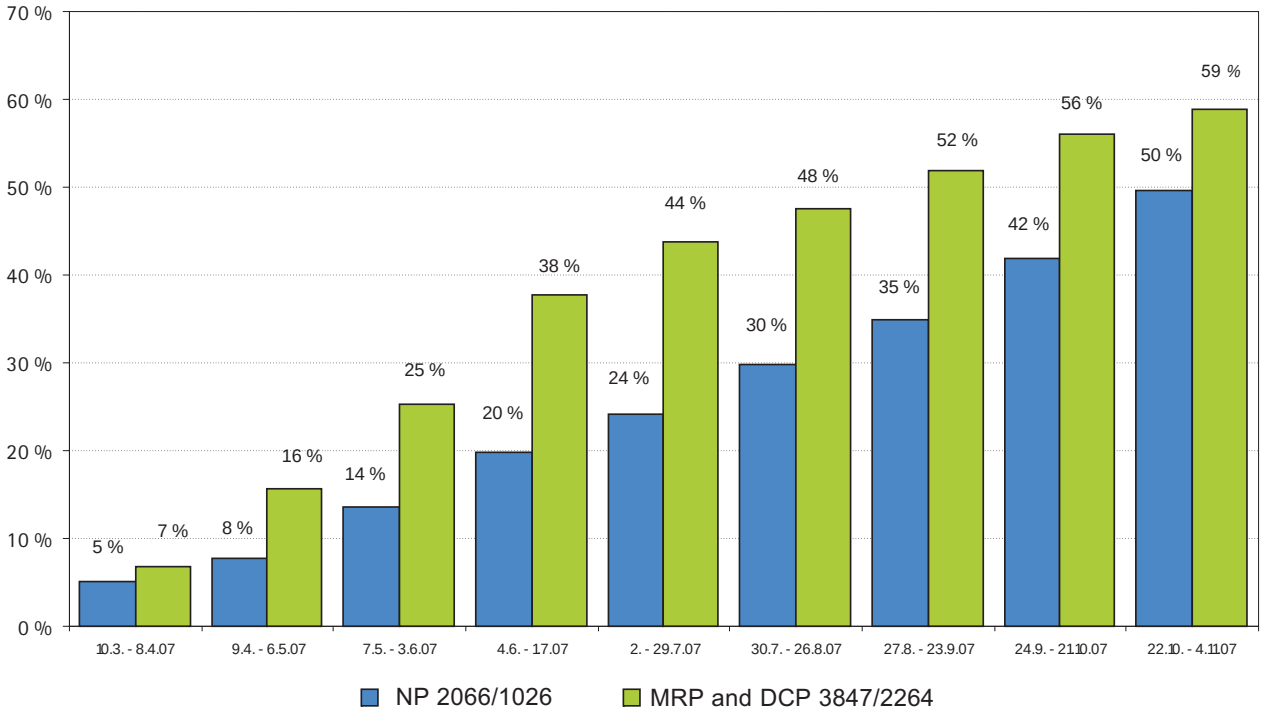

Fig 3. The proportion of applications processed in the project 'JonotPois' is growing in proportion to all applications in the project. NP = national procedure, MRP = mutual recognition, DCP= de-centralised procedure.