School of Pharmacy

Issues with the Use of Medicines in Paediatrics: Off-label and Unlicensed Use, and Formulation Uncertainty

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature:

Date:

Abstract

Background

Many of the drugs prescribed for children are either unlicensed or have been prescribed outside the terms of their product license (off-label). In many of these cases dosages are extrapolated from data obtained from adult trials. Developmental changes that occur with age influence the pharmacokinetic and pharmacodynamic effects of drugs. Because of these effects, data such as efficacy, doses or toxicity extrapolated from clinical studies in adults may be inappropriate for children. Off-label and unlicensed prescribing in paediatrics is a global phenomenon due to a lack of adequate registration of paediatric drugs and formulations. Three small Australian studies conducted in inpatients and a neonatal intensive care unit have provided limited data on the extent of off-label prescribing in paediatrics in Australia. There are no data available in Australia that considers the extent of off-label and unlicensed prescribing in paediatrics in all hospital settings, including inpatients, outpatients and Emergency Department admissions.

Aims

To investigate the extent of off-label and unlicensed prescribing at Princess Margaret Hospital, which is the largest and sole paediatric hospital in Western Australia and to report on the stability of parenterally administered lincomycin used in an unlicensed manner.

Methods

Patient records from Princess Margaret Hospital (PMH) were randomly selected from all 145,550 patients seen at the hospital during 2008. The 1038 randomly selected records for the retrospective study were from 55,591 patients from Emergency Department admissions, 24,425 records from inpatients and 65,534 records from outpatients. Relevant data collected from each medical record included an identification number, type of patient

(inpatient, outpatient or emergency), sex, date of birth, weight, height, diagnosis, adverse effects, past medical history, ceased medications and reasons for ceasing, as well as prescribing details for each drug prescribed including date of prescription, dosage form, dose, strength and frequency of administration. Drugs were classified as off-label using an exclusivity hierarchical system based on age, indication, route of administration and dosage. All drugs were classified according to the WHO Anatomical Therapeutic Chemical (ATC) code. Standard statistical tests were applied.

To provide data for currently used unlicensed formulations, the stability of lincomycin was investigated under accelerated storage conditions and at various pH values. The stability of lincomycin was also tested at 25° C in IV solutions including sodium lactate (Hartmann's Solution), 0.9% sodium chloride solution, 5% glucose solution and 10% glucose solution.

Results

A total of 1037 paediatric patients were included in the study, of which the majority were males (607; 58.5%). The age of patients ranged from newborn up to and including 18 years. Most records (403; 38.9%) were from the Emergency Department (36.6% outpatients; 24.5% inpatients) and a majority in each setting was males (57.8% Emergency Department; 65.4% inpatients; 54.7% outpatients).

A total of 2654 prescriptions for 330 different drugs were prescribed to 699 patients (67.4%). The ATC category with the largest number of drugs was the nervous system (n = 1034; 39.0%). Of all drugs prescribed, 1905 (71.8%) were licensed, 681 (25.7%) were off-label and 68 (2.6%) were unlicensed so the overall extent of off-label and unlicensed prescribing was 28.3%. The ATC categories with a majority of off-label drugs (n = 295; 43.3%) were the nervous system and the alimentary tract (n = 139; 20.4%). The drugs most commonly prescribed in these categories were Painstop®, oxycodone, paracetamol and ondansetron. The ATC categories with a majority of unlicensed drugs were systemic hormonal preparations excluding sex

hormones (n = 22, 32.4%) and sensory organ drugs (n = 13, 19.1%). The most commonly prescribed drugs in these categories were dexamethasone and dilacaine, both of which were hospital formulations.

Inpatients were prescribed more off-label drugs than outpatients or Emergency Department patients ($p < 0.0001$). The highest percentage of off-label prescribing occurred in infants (28 days to 23 months) and children (2 to 11 years) (31.7% and 35.9% respectively) and the highest percentage of unlicensed prescribing (7.2%) occurred in infants (28 days to 23 months). The results were significant ($p < 0.0001$).

The most common reasons for off-label prescribing were dosage (47.4%) and age (43.2%). Overall, the ten most commonly prescribed off-label and unlicensed drugs were ondansetron, Painstop Day®, salbutamol, oxycodone, paracetamol, midazolam, fentanyl, dexamethasone, ticarcillin with clavulanic acid and amoxicillin.

The sample of lincomycin hydrochloride (Lincocin®) under investigation was found to meet the British Pharmacopoeia specifications for lincomycin content. Stability studies of 0.6 mg/mL lincomycin hydrochloride in 0.1 M hydrochloric acid solution, 0.1 M sodium hydroxide solution and 3% hydrogen peroxide solution at 60° C showed that degradation occurred most rapidly in hydrogen peroxide suggesting that lincomycin hydrochloride readily undergoes oxidation. Lincomycin hydrochloride was found to be stable in sodium lactate (Hartmann's) solution, 0.9% sodium chloride solution, 5% glucose solution and 10% glucose solution, with only a small proportion degrading over the 31 day period at 25°C. Lincomycin hydrochloride had the greatest stability at pH 4.00, with a calculated shelf-life of 4.59 days at 80°C. It was least stable at pH 2.00, with a calculated shelf-life of 0.38 hours at 80°C.

Conclusion

This is the first random sample of off-label and unlicensed prescribing from a major teaching hospital. The findings provide a sound assessment of off-label and unlicensed prescribing in Australia. Particularly in inpatients, off-label prescribing was found to be high, with lower levels in outpatients and Emergency Department patients. This indicates that many patients when admitted to hospital will be exposed to drugs, doses or formulations which have not been evaluated for licensing in that paediatric population.

Most of the commonly prescribed off-label and unlicensed drugs have been on the market for many years and have had a lengthy time for evaluation in paediatric patients, yet despite this, adequate data is lacking worldwide. An international evaluation committee should be established to evaluate current published data to provide evidence for efficacy, dosage and adverse drugs reactions in paediatric patients.

Data on the stability of lincomycin hydrochloride have provided some evidence base for its unlicensed administration to children.

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Presentations related to the thesis

Czarniak P, Sunderland V, Chandini V, Parsons R. 2010. Prescribing in a Paediatric Population. Conference presentation. *Annual Conference of the Australian Pharmaceutical Science Association*. Brisbane, December 6 to 9.

Czarniak P, Hughes J, Parsons R, Bint L, Sunderland V. 2012. Off-label and unlicensed prescribing in a Western Australian paediatric population. Conference poster. *Annual Conference of the Australian Pharmaceutical Science Association*. Sydney, December 2 to 5.

Abbreviations used in Thesis

ADR/ ADRs	adverse drug reaction/ adverse drug reactions
AHMAC	Australian Health Minister's Advisory Council
AMH	Australian Medicines Handbook
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical
BP	British Pharmacopoeia
BPCA	Best Pharmaceuticals for Children Act
CNS	central nervous system
EMA	European Medicine Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernisation Act
GLM	Generalised Linear Model
GFR	glomerular filtration rate
HPLC	High Performance Liquid Chromatography
ICU/ ICUs	intensive care unit/ intensive care units
IV	intravenous
MIMS/ eMIMS	Monthly Index of Medical Specialties
MRSA	methicillin resistant *Staphylococcus aureus*
NICU/ NICUs	neonatal intensive care unit/ neonatal intensive care units
NMP	National Medicines Policy
NSAID	nonsteroidal anti-inflammatory drugs
OTC	over-the-counter
PASW	Predictive Analytics SoftWare
PBS	Pharmaceutical Benefits Scheme
PDCO	Paediatric Committee
PeRC	Pediatric Review Committee
PI	Product Information
PIP	Paediatric Investigation Plan
PMAG	Paediatric Medicines Advisory Group

PMH	Princess Margaret Hospital
PONV	postoperative nausea and vomiting
PREA	Paediatric Research Equity Act
QUM	Quality Use of Medicines
RSD	relative standard deviation
SAS	Special Access Scheme
SPC	Summary of Product Characteristics
SPSS	Statistical Package for the Social Sciences
TGA	Therapeutic Goods Administration
TPN	total parenteral nutrition
WHO	World Health Organization

Chapter 1

Objectives and Literature Review

1.1 What the PhD is addressing

Prescribing of off-label or unlicensed drugs exposes patients to medications that have not been independently evaluated for safety, quality and efficacy in that patient population. Infants and children, because of developmental pharmacokinetics and variable weight are more susceptible to adverse effects from such treatments. Although a number of studies have been published these have usually examined specific classes of drugs. This project is designed to describe the prevalence of off-label and unlicensed drug use, to identify drugs most commonly used off-label or unlicensed, and to identify factors associated with off-label or unlicensed drug use in a randomly selected Australian hospital paediatric population. It will also examine variables such as age, dose for age and any reported adverse effects of selected drugs from the study, since many drugs undergo metabolism by enzyme systems that change with age. This study will specifically investigate off-label prescribing in paediatric patients at Princess Margaret Hospital in four age groups defined for the paediatric population.

Further, due to a lack of stability data of lincomycin in IV fluids, this thesis will provide evidence regarding the stability of lincomycin in various buffers and various IV fluids. These data are also useful when formulating preparations with respect to where the optimum pH maximum stability occurs. In addition, it provides essential stability data relevant to the safety of use of lincomycin.

The research work was designed to achieve the following objectives:

- To analyse the prevalence of off-label and unlicensed use of medicines in a Western Australian paediatric hospital with respect to the type of patient and drug classification.
- To analyse the data for those drugs frequently used in an off-label or unlicensed manner.
- To analyse the data for which age groups are most commonly associated with off-label and unlicensed prescribing.
- To determine the stability of lincomycin in solution and in various IV fluids.

1.2 Introduction

In 1999, the National Medicines Policy (NMP) was launched to improve positive health outcomes for all Australians through their access to and judicious use of medicines. The Therapeutic Goods Administration (TGA), which is the regulatory body for therapeutic goods and a division of the Australian Department of Health and Ageing established under the Therapeutic Goods Act in 1989, has a key role in the implementation of the NMP and is responsible for monitoring activities and conducting assessments to ensure that therapeutic goods available in Australia meet acceptable standards. In Australia, it is a requirement that drugs are licensed by the TGA to ensure that all new drugs meet requirements for efficacy, safety and quality.[1] The Australian Register of Therapeutic Goods (ARTG) lists goods that have been evaluated and approved by the TGA. Therapeutic goods are defined as products for use in humans that influence the inhibition or modification of a physiological process; prevent, diagnose, cure or alleviate a disease, ailment, defect or injury or test the susceptibility of persons to a disease or ailment.[2] Drugs to be listed on the ARTG require a sponsoring company to make an application with supporting data on the quality, safety and efficacy of the product for its intended use.[3] A similar process must be followed for paediatric drugs listed on the ARTG. Any goods that are not listed are unregistered or unlicensed medicines. The term "unregistered" is often used interchangeably with "unlicensed" as overseas, drug approval is usually through a licensing process whereas in Australia, the process is one of registration.

Many of the drugs used in children have either been not licensed for use in children (unlicensed) or have been prescribed outside the terms of their product license (off-label prescriptions) and dosages are often extrapolated from data obtained from adult trials.[4] Developmental changes that occur with age influence the pharmacokinetic and pharmacodynamic effects of drugs. Because of these effects, data such as doses or toxicity extrapolated from clinical studies in adults may be inappropriate for children.[5]

1.3 Pharmacokinetic and pharmacodynamic changes in paediatrics

Pharmacokinetic responses to drugs, such as drug absorption, metabolism, distribution and elimination, are substantially different in children compared to adults. These responses change with growth and maturation. For regulatory purposes, the International Commission on Harmonisation has defined the paediatric population into five distinct groups which broadly represent the ages at which the major changes in physiological, pharmacokinetic and pharmacodynamic parameters occur during development. These groups include preterm newborn infants (< 37 weeks gestation), term newborn infants (zero to 27 days), infants and toddlers (28 days to 23 months), children (two to 11 years) and adolescent (12 to 16 or 18 years of age, dependent on region).[6]

1.3.1 Absorption

Developmental changes in the paediatric population can affect the rate and extent of absorption from the gastrointestinal tract. As an infant grows into an adult, these factors undergo considerable maturational changes. In the newborn infant, the gastric pH is alkaline (pH 6 to 8) and changes to an acidic pH (1.5 to 3) over the next 24 hours.[7] Acid concentrations and the volume of gastric juice do not reach adult levels until after two years of age and can influence the bioavailability of drugs. For example, H_2-antagonists such as ranitidine can increase gastric pH and reduce the bioavailability of acidic drugs such as itraconazole whereas orange juice and carbonated drinks decrease gastric pH and increase the bioavailability of acidic drugs.[7] Milk and infant formula can also decrease the absorption of acidic drugs by increasing gastric pH. Gastric emptying rate is considerably delayed in infants and does not reach adult levels until six to eight months of age. Since most orally administered drugs are absorbed from the small intestine, the shorter gastric emptying time leads to a faster rate of absorption.[7]

1.3.2 Distribution

Volume of distribution of drugs in children changes with age because of changes in body composition (especially the extracellular and total body water spaces) and plasma protein binding. Body composition changes most dramatically during the first year of life but changes continue through puberty and adolescence, especially in terms of total body fat.[8] In a full-term neonate, total body water is approximately 75% and decreases to 60% (25% is extracellular and 35% is intracellular water) by one year of age. Adult values of 50 to 60% (20% extracellular and 40% intracellular water) are not reached until about 12 to 13 years of age.[7] Due to the relatively large extracellular and total body water spaces in neonates and infants compared to adults, hydrophilic drugs such as aminoglycosides, have larger apparent volumes of distribution but lower plasma concentrations for the same weight-based dose.[8] Therefore, in order to achieve recommended peak concentrations of aminoglycosides, larger milligram-per-kilogram doses are required.[7] At full-term, total body fat makes up 12 to 16% of body weight and increases to 20 to 25% at one year of age. Total body fat increases rapidly in females at puberty and approaches twice the value of body fat compared to males. Therefore, children and adults will have a larger volume of distribution of lipophilic drugs than neonates and infants due to a higher percentage of body fat.[7]

Plasma protein binding is altered in neonates and young infants due to the amount and composition of circulating plasma proteins. The important drug-binding proteins include albumin, lipoproteins and alpha-1-acid glycoprotein. On average, albumin makes up 58% of all plasma proteins but in neonates and infants, the quantity of albumin and total plasma proteins are reduced.[8] Adult values of the total protein concentration including serum albumin and alpha-1-acid glycoprotein are not reached until one year of age and remain consistently stable in healthy children between two and 18 years of age.[7] Binding affinity for albumin is pronounced for acidic and neutral drugs such as digoxin, warfarin and beta-lactam antibiotics. Basic drugs such as propranolol bind to lipoproteins and alpha-1-acid glycoprotein.[7] Only the free

fraction of drug, i.e. non-protein bound drug in the plasma, is able to distribute to its site of action. For drugs that are highly protein bound, only a small percentage will exist as the free fraction. Hence small changes in the binding of the drug can make a large difference to the free drug concentration.[8]

1.3.3 Metabolism

The liver is the principal organ of drug metabolism but the kidneys, intestine, lungs and skin may also be involved. Most drugs that are metabolised are converted to more water-soluble compounds for enhanced excretion from the body by the kidneys.[9] At birth the majority of enzymes are either absent or present in considerably reduced amounts compared with adult values and evidence indicates that the various systems do not mature at the same time.[10]

The two main enzyme systems involved in drug metabolism are phase I and phase II reactions. Phase I reactions include hydrolysis, reduction, oxidation and hydroxylation that usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group for a phase II conjugation reaction.[9] In phase II reactions, the substrate may be conjugated with endogenous agents such as glutathione, glucuronic acid, glycine, acetate and sulfate to produce a more polar compound that can be eliminated easily by the renal and/or the biliary system.

The cytochrome P450 family are the most important phase I enzymes with CYP1, CYP2 and CYP3 genes being important in human drug metabolism. The activity of a number of cytochrome P450 enzymes, including CYP2D6, CYP2C19, CYP2C9 and CYP3A4 is significantly reduced in the neonate. The activity of CYP3A4 in neonates is 30 to 40% that of adult activity, reaches an adult pattern by six months of age, increases between the age of one to four years and then gradually changes to adult levels during adolescence. The activity of CYP2C9 is reduced in the neonate, reaches adult levels by one to six months of age, increases with peak activity from three to 10 years and

decreases to adult values at puberty.[7] This has the potential for pharmacokinetic consequences when drugs act as substrates for these enzymes. For example, phenytoin is a substrate for CYP2C9. In preterm infants, the elimination half-life of phenytoin is approximately 75 hours, decreases in term infants to 24 to 48 hours and in infants two weeks after birth, it decreases further to approximately eight hours.[8]

The phase II enzymes consist of sulfotransferases, glucuronosyltransferases, arylamine N-acetyltransferases, methyltransferases and glutathione S-transferases, all of which play an important role in biotransformation of drugs.[7] Important differences exist between children and adults, and phase II enzymes do not follow the same development patterns.

The reduced metabolism rates at birth are followed by a dramatic increase in metabolism rates in the older infant and young child, and the metabolic clearance of many drugs, including carbamazepine, phenytoin and theophylline, in the one to nine year age group is greater than in adults.[10]

1.3.4 Elimination

Excretion of drugs or their water soluble metabolites is mainly via the kidneys. Developmental changes in renal function, especially glomerular filtration, tubular secretion and reabsorption all impact on the renal elimination of drugs.[7] There is a dramatic increase in glomerular filtration rate (GFR) from birth due to changes in renal blood flow and GFR approaches adult values by approximately three to five months of age.[7, 8] Renal tubular secretion increases more slowly but at eight to 12 months of age both glomerular and tubular function are close to values seen in adults.[8] Renally excreted drugs, especially those with a narrow therapeutic range, should be based on the patient's renal function to avoid toxicity due to decreased elimination and increased accumulation.[7]

1.3.5 Pharmacodynamics

Studying the pharmacodynamic effects of interactions between drugs and receptors in younger patients may be difficult although for some conditions, it may be relatively straightforward, e.g. seizure control in a child with epilepsy. For others, e.g. assessment of pain relief in neonates, it may be much more challenging. Pharmacodynamic determinants may also be related to age-dependent differences in the severity of adverse drug reaction (ADRs) such as increased liver toxicity of valproic acid in infants.[8]

The choice and dosage of medicines in various age groups is influenced by developmental changes that affect the bioavailability, pharmacokinetics and pharmacodynamics of drugs, especially in early childhood. In children, in many cases the only medicines available have not been clinically tested for safety, efficacy and dosage for the age group for which they are used.[8]

1.4 Past tragedies

Several drug-related tragedies spurred the introduction of drug licensing processes around the world to ensure that drugs were shown to be safe and effective for their specific indications.[11] In 1937 the death of 107 people, mainly children, was attributed to ingestion of sulfanilamide elixir that used diethylene glycol, also known as antifreeze, as a solvent.[12, 13] No toxicity testing had been done on the product prior to marketing.[14] The mechanism of some drug-related tragedies has been explained through pharmacokinetic studies, such as kernicterus after use of sulfonamides and gray baby syndrome after use of chloramphenicol.[15] In neonates and infants with increased erythrocyte destruction and limited liver capacity for conjugation, bilirubin levels may be increased. Due to a decreased binding capacity of bilirubin to plasma albumin, bilirubin may be displaced from plasma protein binding sites by drugs that are highly bound to plasma proteins such as sulphonamides, thereby contributing to kernicterus.[7] Kernicterus results from

the penetration of bilirubin into the central nervous system (CNS) nerve tissues and damages mitochondria.[16] Gray baby syndrome has caused deaths in neonates treated with chloramphenicol when doses which exceeded the underdeveloped hepatic metabolism of the neonate were used.[17] Chloramphenicol is eliminated via two important mechanisms - inactivation through conjugation with glucuronic acid and excretion of free chloramphenicol by glomerular filtration and the glucuronic acid conjugate by tubular excretion. In the newborn, deficiencies in the conjugating system and poor renal function result in toxic levels of chloramphenicol.[17, 18]

In the United States (US), the Drug Laws of 1962 were introduced after the thalidomide catastrophe, which resulted in foetal malformations after exposure of the unborn foetus to thalidomide during pregnancy.[14, 19] By 'legal' definition, drugs introduced since 1962 had to be safe and effective in the population for which they were to be marketed.[19] The safety and efficacy in one population could not be transferred to another. Thus safety and efficacy in adults cannot be applied to children.[14] Despite these laws, children have often been likened to 'therapeutic orphans', a term first coined by Shirkey in 1968 due to the lack of pharmacokinetic, pharmacodynamic, efficacy and safety studies necessary for this population to be provided with safe and effective drug therapy.[19]

1.5 Criteria for off-label and unlicensed prescribing

Unlicensed and off-label prescribing is not illegal and may sometimes be clinically appropriate. However, the definition of off-label and unlicensed drug use of medicines varies across the literature, with some studies considering only one type of off-label use and others considering up to seven.[20] The methods used to assess off-label and unlicensed prescribing also vary between studies, making direct comparisons difficult.[21]

The most common definitions, as used by Turner et al.[22-24], describe off-label drug use as the use of a registered drug in a manner not listed in the approved product license with respect to age, dose, indication or route of administration. Some researchers also include drugs that are used when contraindicated in the definition of off-label.[25]

Medicines may be prescribed outside the age range for which they are licensed by regulatory authorities. For example, the product information for midazolam, a benzodiazepine with anxiolytic properties, states that safety and effectiveness in children below the age of eight years have not been established.[26-29] Despite this, midazolam is frequently used off-label in children below this age.[22-24]

Medicines may be given at doses higher or lower than the approved range or they may be administered more frequently than approved. For example, the product information for salbutamol metered dose inhaler states that the adult and child dose is one to two inhalations, which may be repeated every four hours. In the hospital setting, higher frequencies are often used, in the range of six to 12 inhalations administered half hourly to four hourly, which is then off-label use.[22-24]

Medicines may be used for indications that are not stated in the approved product information. While medicines are initially registered for specific indications, circumstances may arise where the drug is used for treating other conditions. Supporting evidence at various levels of validity for additional indications may have been reported in the literature but often the manufacturer's product information is not updated to reflect this. For example, clonidine is indicated for hypertension, migraine or recurrent vascular headache prophylaxis and menopausal flushing, however, in children it is often used as an analgesic or in the treatment of Attention Deficit Disorder.[30] Despite not being approved for these indications in children, several studies have supported its benefits in the literature.[31, 32]

Medicines may be administered by an unapproved route for a particular formulation. For example, to avoid pain and discomfort to a patient, an injection solution may be administered orally rather than parenterally. This usually involves breaking an ampoule and administering the solution by mouth (e.g. midazolam injection administered orally) or as inhalation (e.g. tobramycin injection used as inhalation in cystic fibrosis).[22-24]

Manufacturers often add disclaimers in the product information regarding the use of a drug in children, which can complicate the designation of the drug as off-label. For example, the product information for clobazam states that the drug is 'not recommended for children', despite evidence in the literature to support its use for seizures in children.[30, 33] These types of disclaimers and absence of guidance were described by Shirkey more than 40 years ago as 'orphaning' clauses.[19]

According to Turner et al.[22] an unlicensed drug is defined as the use of medicines without a product license or marketing authorisation. Categories of unlicensed drug use include formulation modifications to licensed drugs, drugs that are licensed but manufactured in a particular formulation under a special license, use of chemicals as drugs, new drugs available under a special manufacturing license, drugs used before a license has been granted and imported drugs (where a drug is licensed in another country).[22]

Modification to or reformulation of registered (licensed) drugs is usually considered as producing an unlicensed formulation, which would not be registered with the TGA. Many licensed adult dosage forms, such as tablets and capsules, are inappropriate for use in children because they cannot easily be swallowed. A study by Tan et al.[34] reported that, despite specific paediatric dosing information being provided in the Australian Monthly Index of Medical Specialities (MIMS)[30], many of the medicines were not available in dosage forms appropriate for children. In order to obtain a suitable dose, crushing licensed tablets or opening a capsule and using the contents to prepare a suspension may be used.[35] For example, preparing an omeprazole suspension from tablets or capsules (both of which are registered

formulations of omeprazole) would produce an unregistered (unlicensed) formulation which has not been approved by the TGA.[24]

Medicines may be prepared extemporaneously by pharmacists compounding raw ingredients/chemicals according to a formulation published in a pharmacopoeia (e.g. British Pharmacopoeia)[36] or other reference (e.g. Australian Pharmaceutical Formulary and Handbook).[35, 37] However, relevant pharmaceutical analysis or quality assurance data, as well as bioavailability data and information on the stability of the product, is usually limited or not available.[38] A study in the UK investigating the inter-hospital constancy of captopril formulations used to treat children with heart failure, found that a wide variety of unlicensed and untested liquid captopril formulations were used interchangeably without sufficient evidence of bioequivalence.[39]

Pharmacists can prepare medicines extemporaneously. As part of the Therapeutic Goods Regulations 1990, compounding of formulations for an individual patient and an individual purpose by a pharmacist is excluded from the registration requirements of the Therapeutics Goods Act 1989.[2] However, unlicensed drugs can also be prepared extemporaneously by TGA-licensed manufacturers of therapeutic goods. Novel formulations, such as caffeine injections for apnoea of prematurity may not be commercially viable for a manufacturer to take through the regulatory process, so licensed manufacturers in hospitals, that provide a greater level of quality assurance, are able to prepare a range of paediatric products.[24]

In some circumstances, when there is no registered drug available and no pharmaceutical material of recognised standard, a non-pharmacopoeial substance or chemical may be used as a medicine.[24] Examples include copper and zinc sulfate as dietary supplements and arginine used in the management of metabolic disorders.[1, 24]

In some situations, where patients require access to therapeutic goods that are not listed on the ARTG, access may be obtained through the Special Access Scheme (SAS). The SAS provides access to unregistered drugs

which are awaiting approval in Australia or which may be registered overseas and unlikely to be registered in Australia on a single patient basis. With the exception of drugs of abuse, any unapproved therapeutic good can potentially be supplied by the SAS.[40] 'Personal Importation' also allows an individual to import unapproved therapeutic goods for personal use, unless prohibited by other laws.[41]

1.6 Studies in off-label and unlicensed prescribing

Unlicensed and off-label prescribing is a global phenomenon particularly involving paediatric drugs and formulations. The use of off-label and unlicensed medicines is usually reported in two ways. The percentage of studied children who have been given at least one off-label or unlicensed medication describes the prevalence whereas the percentage of individual prescription items that meet off-label or unlicensed criteria describes the frequency (or extent) of off-label and unlicensed prescribing. The extent of off-label and unlicensed prescribing in paediatrics has been reported to range from 7 to 60%, with 28 to 100% of paediatric patients receiving at least one off-label or unlicensed drug.

Several retrospective and prospective studies have been conducted in different countries across the world. A summary of 35 studies that have reported the frequency of off-label or unlicensed prescribing from different patient types and various hospital settings including outpatients in a general paediatric ambulatory unit, medical and surgical wards, wards with several different paediatric specialities such as respiratory, gastroenterology, cardiology, neurology, nephrology, neonatal intensive care units (NICUs), medium care units, paediatric intensive care units, oncology inpatients and outpatients and Emergency Departments is provided in Appendix 1. Most of the studies were prospective (n = 25) and study periods ranged from four weeks to three years. The number of patients investigated ranged from 34 to 1,708,755 and age ranged from preterm and newborn to 20 years, although

in one study 23 adult patients aged between 19 to 40 years were included.[42] Some studies have involved only specific patient types e.g. neonates or infants,[1, 11, 43-45] oncology patients, gastroenterology or pain management.[46-49] Some studies investigated adverse drug reactions associated with off-label or unlicensed drug use.[23, 50] In the hospital setting, the proportion of children that receive off-label or unlicensed drugs has been shown to be higher in intensive care units (ICUs) and in those with complex diseases.

1.6.1 Studies in NICUs and other ICUs

The highest prevalence of off-label and unlicensed prescribing has been reported in ICUs.[1, 11, 23, 43-45, 51] Only five studies in the UK, France, Australia, Israel and Italy were exclusively in NICUs.[1, 11, 43-45] The percentage of off-label prescriptions reported in these five studies ranged from 47 to 63% and the percentage of unlicensed prescriptions ranged from 10 to 16%. The studies, conducted over four weeks to four months, included between 34 to 105 neonates, found that the number of patients receiving off-label or unlicensed drugs ranged from 51% to 90% although in one study 93% of patients received off-label drugs.[45]

In a prospective 13 week off-label and unlicensed study of patients admitted to neonatal intensive care in the UK, 70 patients (of which 49 were premature babies) received a median of 3.5 prescription episodes.[43] Of the total 455 prescription episodes, 54.7% were off-label, 9.9% were unlicensed and 90% of babies received at least one off-label or unlicensed drug. The ten most commonly administered drugs were gentamicin, benzylpenicillin, folic acid, Dalivit® (multivitamins), albumin, vitamin K, frusemide, caffeine, flucloxacillin and morphine. The most common off-label and unlicensed drugs were benzylpenicillin, folic acid, Dalivit® (multivitamins), vitamin K, caffeine, flucloxacillin, albumin, gentamicin, morphine, glycerin, sodium chloride, total parenteral nutrition (TPN). The authors concluded that off-label and unlicensed prescribing in the neonatal intensive care setting was far greater than in older children.

Similar findings were reported in a prospective study in a NICU in France which included 40 babies with a gestational age between 25 and 40 weeks, of which 88% preterm newborns had a birth weight lower than 100g.[44] A total of 257 prescriptions, involving 55 different medicines, were administered, mostly antibacterial drugs, analgesics and drugs for respiratory diseases. Of the prescribed drugs, 62% were off-label for premature infants and 64% for newborns, most being off-label for age. The researchers reported that there were no therapeutic alternatives available. Testing drugs for registration for premature babies is very limited and guideline development in this situation may be a better option.

Other studies have reported similar findings. A ten week prospective study involving 97 infants (with a gestational age was between 23 to 41 weeks) in a NICU in Australia, reported the median number of prescriptions that each infant received was seven.[1] Of the total number of 1442 prescriptions (involving 69 different drugs), 47% were off-label, 11% unlicensed and 80% of infants received an off-label or unlicensed drug or both, but this proportion rose to 93% in extremely low birth weight infants. The ten most commonly used drugs were gentamicin, morphine, vancomycin, benzylpenicillin, theophylline, aminophylline, frusemide, vitamin K, 6% sodium chloride and phosphate. The most frequently used off-label drugs were morphine (for which the safety and efficacy in neonates have not been established), theophylline (which is not indicated for prevention or treatment of apnoea of prematurity), aminophylline (which is not indicated for prevention or treatment of apnoea of prematurity), phosphate (which is not indicated for prevention or treatment of osteopenia of prematurity), dobutamine (which is not indicated for treatment of hypotension in neonates), paracetamol (administration to infants under one month of age is not recommended), dopamine (which is not indicated for treatment of hypotension in neonates) and phenobarbitone (which is not recommended in neonates). The most frequently used unlicensed drugs were 6% sodium chloride, which was an 'in-house' product, and spironolactone, which was unlicensed due to modification of a licensed product. The researchers reported that in Australia, as in the UK, the incidence of off-label and unlicensed prescribing in NICUs was greater than

among patients on general medical and surgical wards. The researchers stated that the frequency with which some drugs, such as morphine, methylxanthines and inotropes were used in an off-label or unlicensed manner, without other suitable alternatives, highlighted the need for the provision of evidence based data or registration.[1]

A two month prospective study involving 19 preterm and 15 term newborns in Italy reported a median of 5.5 prescriptions per patient.[11] Of 176 prescriptions, 12% were unlicensed and 50.5% off-label. Drugs most frequently used off-label and unlicensed included parenteral nutrition infusion, amikacin, ranitidine, tobramycin, ofloxacin, calcium levofolinate, caffeine and sodium ferric gluconate complex. The most common cause for use in an off-label manner was that a higher dose than recommend by the manufacturer was used and related mainly to systemic antibiotics.[11]

Similar findings were also reported from Israel where a prospective study in a NICU where 105 neonates were reviewed every two weeks during a four month period.[45] Researchers reported that of 525 medications administered, 59% were off-label and 16% unlicensed. Further, 93% of patients received at least one off-label medication. The main reasons for off-label prescribing were dose and age. Drugs prescribed off-label or unlicensed included ampicillin, theophylline, gentamicin, cisapride, morphine, cimetidine, frusemide, spironolactone and thyroxine sodium.[45, 52]

1.6.2 Other studies

Other studies have been carried out across several ward categories including the NICU. A prospective 13 week study in the UK involved patients from five wards covering a variety of different paediatric specialities and studied 4455 drug courses administered to patients aged between one day and 18 years.[23] The median number of drug courses was three and although this study did not distinguish between off-label and unlicensed prescribing, overall 35% of drug prescriptions were off-label or unlicensed and 48% of the 1046 patients received one or more off-label or unlicensed drugs. The highest incidence of

off-label and unlicensed prescribing was in the ICUs, especially the NICU, which reported 55% of off-label and unlicensed prescriptions.[23] The most common drugs used off-label or unlicensed were not reported because the study focused on ADRs associated with off-label and unlicensed use.

A study from the Netherlands across different wards including the NICUs, reported a higher incidence of unlicensed prescribing.[53] A five week prospective study conducted in four hospital units (wards) reported the incidence of unlicensed prescribing as 62% (which was higher than reported in other studies) and off-label prescribing as 14% in the neonatal ICU. The researchers found that 90% of patients received at least one off-label or unlicensed drug. Although the most frequently encountered unlicensed and off-label drugs were cisapride, caffeine and tobramycin, in the NICU, the most frequently used unlicensed and off-label drugs were caffeine, vitamins D_3 and E, ipratropium and salbutamol, tobramycin and dexamethasone.[53] Another prospective study by the same researchers, which did not include patients from the NICU but in which data for 293 patients (aged zero days to 16.7 years) from a paediatric ward and neonatology unit were recorded daily over a five month period, also reported a relatively high incidence of unlicensed prescribing with 28% of drugs unlicensed and 44% off-label. Further, the number of patients receiving one or more unlicensed and off-label drugs was higher in newborns and small infants (98% of patients in these age groups compared with 88% in all children). In this study, the most commonly prescribed unlicensed and off-label drugs to all children were paracetamol, cefotaxime, amoxicillin, caffeine, vitamin K, cisapride, folic acid, ipratropium/salbutamol, salbutamol and budesonide.[54] Importantly, the researchers stated that the reason for the high percentage of unlicensed prescribing in the Netherlands was that hospital pharmacies were allowed to manufacture medications (i.e. home-label) and modify commercial preparations to make them suitable for administration to children. The high use of home-label medications (41%) was attributed to the lack of commercially registered flexible paediatric formulations.

In a four month prospective study of the use of off-label and unlicensed medicines in the UK in a Paediatric ICU, 166 patients (aged one day to 15 years, 52% less than one year old) received a median of three drugs in 862 different episodes.[51] Of these 268 (31%) involved drugs that were off-label or unlicensed and 70% of patients received at least one off-label or unlicensed drug. Drugs prescribed in an off-label or unlicensed manner included morphine, midazolam, chloral hydrate, sucralfate, adrenaline injection, dopamine injection and amiloride solution.[51]

A high prevalence of off-label and unlicensed prescribing has also been reported in hospital settings in Europe. In a prospective study conducted over six months in Switzerland involving 60 randomly chosen paediatric inpatients (aged three days to 14 years) from six different wards from two hospitals, of the 483 prescriptions reviewed, 51% followed the terms of the marketing authorisation but 25% were off-label and 24% were unlicensed. [55] The ten most frequently prescribed off-label and unlicensed drugs were morphine, sodium chloride injection, heparin, spironolactone, hydrochlorothiazide, ondansetron, captopril, mefenamic acid and potassium chloride injection. Patients in paediatric intensive care, who had more complex therapy, had the highest prevalence of off-label or unlicensed prescribing (58%). This study found that all patients received at least one off-label or unlicensed drug but infants and toddlers (one to 23 months) received more unlicensed drugs (33%) than other groups.[55]

Off-label and unlicensed prescribing was also found to be common in Finland.[20] A two week prospective study involving 141 children (aged under 18 years), reported 629 prescriptions were received by 108 children of which 36% were off-label and 13% were unlicensed. In this study, 76% of children received at least one off-label or unlicensed drug. A greater percentage of children in the surgical ward (91%) than in the NICU or general ward received off-label or unlicensed drugs (79% and 63% respectively).[20]

In a recent eight week prospective study in Malaysia involving 194 patients (aged between one day to 16 years) from a NICU, paediatric ICU and a

paediatric high dependency unit, a total of 1295 drugs were prescribed. Of these, 34.1% were off-label and 27.3% were unlicensed.[56] Overall, 92% of patients received at least one off-label or unlicensed drug (82% received at least one off-label drug and 44% received at least one unlicensed drug). Children younger than two years were more likely to receive an unlicensed medicine compared to older children. The three most common off-label drugs were gentamicin, paracetamol and glycerin suppositories. The three most common unlicensed drugs were ferric ammonium citrate, caffeine solution and folic acid syrup.[56]

1.6.3 Specialised wards

Although studies conducted mainly in ICUs have reported a high proportion of children receiving off-label or unlicensed drugs (80 to 100%), studies conducted on children in specialised wards, such as cardiology, respiratory and oncology, have also reported a high prevalence of off-label and unlicensed prescribing.[4, 42, 46] In a prospective study in the UK involving 51 paediatric oncology patients (aged 0.6 to 16.3 years) with acute lymphoblastic leukaemia and other malignancies, inpatient and outpatient prescriptions were analysed for four weeks.[46] Of 569 prescription episodes, 26% were off-label and 19% were unlicensed. All patients received at least one off-label drug and the maximum number of off-label or unlicensed drugs was 13. With respect to unlicensed drugs, 16% required modification to produce a suitable preparation that could be administered to a child. Drugs included mercaptopurine, methotrexate, thioguanine and etoposide. Although these drugs have been the mainstay of treatment since 1980 and are likely to continue to be for some time, no suitable formulations for children have been licensed in over 20 years.[46]

In a prospective two year study in Belgrade in a paediatric cardiology ward involving 544 children (aged four hours to 18 years), 76% of patients were prescribed one or more off-label or unlicensed drugs.[4] Of 2037 prescription items, 11% were unlicensed and 47% were off-label for age or dose. Researchers reported that unlicensed drugs were used mostly in children

over two years of age and although unlicensed drugs were not prescribed to neonates, they received most of the off-label drugs (64%). Overall, the greatest number (72%) of off-label (55%) and unlicensed (17%) prescriptions was given to children aged from two to 11 years.[4]

In a prospective six month study in Germany of paediatric respiratory and cardiology wards, of 417 patients aged one day to 40 years (median age was 3.6 years; 23 patients > 18 years), 61% of patients received at least one off-label prescribed drug.[42] Of 1812 prescriptions, 31% were off-label. The highest percentage of off-label prescriptions was for cardiovascular drugs, including beta blockers, diuretics, calcium channel blockers, antiarrhythmics, vasodilators and antithrombotic agents, with 34% off-label for age.[42] Although this study included 23 (6%) adults which could have reduced the rate of off-label prescribing, the findings were similar to those reported in Belgrade by Bajcetic et al. who found that 44% of all cardiovascular drugs prescribed to paediatric patients were off-label.[4]

Studies investigating specific drug groups in the hospital setting have also reported significant off-label or unlicensed prescribing. In a four week study investigating the nature of unlicensed and off-label analgesic agents in children, it was found that of 715 prescriptions episodes analysed, 33% were off-label but none was unlicensed.[49] Although paracetamol was the most common analgesic used, it was off-label for 30% of prescriptions. Pethidine was always used off-label, while diclofenac and morphine were off-label 98% and 79% of the time, respectively. The most common reason for off-label prescribing was dose. The number of patients included in the study and the percentage receiving off-label prescriptions was not included in the study.[49]

1.6.4 Other hospital wards

Several studies have been conducted in medical and surgical wards. In a 13 week prospective study in the UK of 609 paediatric patients aged four days to 20 years, 2013 courses of drugs were administered of which 25% were either off-label or unlicensed.[22] The researchers reported 36% of patients received

one or more off-label or unlicensed drugs. The ten most commonly prescribed off-label or unlicensed drugs were different in the surgical and medical wards. In the surgical ward, they included diclofenac, morphine, oxybutynin, paracetamol, ranitidine, sodium bicarbonate, sucralfate, cisapride, folic acid and Klean-prep® (macrogol 3350 plus electrolytes). In the medical ward, salbutamol, ipratropium, folic acid, multivitamin drops, cisapride, paracetamol, frusemide, dill water, amiloride and TPN were most commonly prescribed off-label and unlicensed.[22]

Similar findings were reported in a prospective study involving 200 paediatric patients in surgical and medical wards in Australia with 36% of patients reported as receiving one or more off-label or unregistered drugs and 16% of drugs off-label or unlicensed.[24] In the surgical ward, which included urology, ear, nose, throat and abdominal surgery, the most commonly prescribed drugs were paracetamol, morphine, metronidazole and ceftriaxone, whereas the most commonly prescribed off-label and unlicensed drugs were metoclopramide, Colonlytely® (macrogol 3350 plus electrolytes), ondansetron and clonidine. In the medical ward, which included renal, cardiology and neurology, the most commonly prescribed off-label and unlicensed drugs were chloral hydrate, aspirin, ciprofloxacin and sodium bicarbonate.[24]

Similar findings were reported in Croatia.[57] In a 12 month prospective study (performed on one predetermined day each month) involving several different wards and 691 patients (aged one day to 20 years), 1443 prescriptions for 198 different drugs were prescribed for 531 patients. Of these, 13.3% were off-label and 11.9% unlicensed. Almost half of the patients (47.8%) received either off-label or unlicensed drug. Wards with the most frequent off-label and unlicensed prescribing were neonatology, intermediate care, ICU, haematology and oncology but the highest prevalence of off-label and unlicensed drug use was in the neonatology ward. The five most frequently prescribed off-label drugs were pantoprazole, esomeprazole, ranitidine, oxymetazoline and granisetron and the five most frequently prescribed unlicensed drugs were nystatin, captopril, trivalent iron, macrogol and valproic acid.[57]

Studies in paediatric medical wards in Europe have reported a higher incidence of off-label and unlicensed prescribing. A four week prospective study to determine the extent of off-label and unlicensed prescribing in paediatric medical wards in five European countries (UK, Sweden, Germany, Italy and the Netherlands) involved 624 paediatric patients aged four days to 16 years.[58] This study found that 46% of 2262 prescriptions were off-label (39%) or unlicensed (7%) and 67% of children were reported as receiving an unlicensed or off-label drug prescription during their stay in hospital. The wards in the countries differed in several ways. The paediatric wards in Germany and Sweden had general paediatric and respiratory cases, whereas in the UK and Italy, wards admitted mainly general paediatric patients (the UK also included children with surgery) and in the Netherlands, the ward had mainly patients with cardiac, renal, oncology and respiratory disease and few general paediatric cases. Consequently, the prescribing habits of the five countries was reported as very different with the most widely prescribed drug in the UK, Sweden, Germany and the Netherlands being paracetamol but in Italy it was beclomethasone. The five most frequently prescribed drugs differed for each country but included salbutamol in four countries (UK, Sweden, Germany and Netherlands) and paracetamol in three countries (Sweden, Germany and Italy). The commonest reason for off-label drug use in Sweden, Germany and Italy was dose and frequency and in the Netherlands, it was formulation.[58]

Studies in Brazil have also reported a high incidence of off-label and unlicensed prescribing.[59] In a five month prospective study in Brazil in a paediatric public hospital ward with several different paediatric specialities including respiratory, gastroenterology, cardiology, neurology and nephrology, researchers reported the extent of off-label and unlicensed prescribing as 45.1% with 82.6% of children receiving at least one unlicensed or off-label drug. There were 17% of patients that received both an unlicensed and off-label drug. The study included 272 patients (aged one month to 14.4 years) and a total of 1450 prescriptions. The ten drugs most frequently prescribed off-label were folic acid, cimetidine, ceftriaxone, phenobarbitone, vancomycin, metoclopramide, ceftazidime, digoxin,

amikacin and dexchlorpheniramine. Age/ weight was the most common reason for off-label prescribing in children under one year of age. The three most commonly prescribed unlicensed drugs were captopril, nifedipine and ursodeoxycholic acid.[59]

In the US, a six month prospective study in a paediatric general ward investigating only off-label drugs, in which 1383 prescriptions were assessed for 403 patients (aged three days to 18 years), 31% were reported as off-label.[60] In this study, off-label drug use was defined according to indication and age. The most commonly prescribed medications that lacked an approved indication for children were ondansetron, salbutamol and ranitidine and the most commonly prescribed medications that were off-label due to age were ketorolac, salbutamol and fluticasone.[60]

In a retrospective multicentre study in the US investigating only off-label prescribing, data from 31 tertiary care paediatric hospitals were collected for 355,409 patients via the Paediatric Health Information System, an administrative database that contains inpatient data from 31 not-for-profit tertiary care hospitals.[61] In this study, 78.7% of hospitalised paediatric patients were found to have received at least one off-label medication but the researchers defined off-label drug use based solely on age criteria (i.e. off-label use was defined as use of a specific drug in a patient younger that the Food and Drug Administration approved age range for any indication of that drug). Drugs that were commonly prescribed off-label included morphine, midazolam, fentanyl, neostigmine, nystatin, bacitracin, metoclopramide, dopamine, bumetanide, spironolactone and potassium chloride. Patients receiving an off-label drug were more seriously ill and thus more likely to receive an off-label medication compared to patients that were less seriously ill.[61]

A recent retrospective study in Australia investigated only the extent of off-label prescribing for 887 prescriptions for 106 different drugs.[62] The extent of off-label prescribing was 32%. The study involved 300 patients (aged one day to 11 years) admitted to a general paediatric ward. Drugs were more

likely to be off-label because they were prescribed at a dosage or frequency greater than approved for the patient's age or weight. The most commonly prescribed drugs were paracetamol, ibuprofen and oxycodone. The ten most commonly prescribed off-label medications were paracetamol, ibuprofen, oxycodone, ondansetron, salbutamol, amoxicillin, flucloxacillin, cephazolin, benzylpenicillin and prednisolone. There were 57% that received at least one off-label medication. The extent of off-label prescribing in this Australian study in Tasmania was found to be higher than reported previously in a study conducted in a paediatric hospital in Western Australia where 36% of patients received off-label or unlicensed drugs.[24] However, the results were markedly lower than the 80% reported by O'Donnell in a NICU in Melbourne, Australia.[1]

Many studies in hospitals have involved specialised centres. However, a prospective study in Ireland in a non-specialised paediatric unit (ward) in which drug prescription charts were examined from 74 paediatric patients (aged one week to 13 years) on one day per week over two months, 3.4% of drugs were reported as unlicensed and 19.4% as off-label.[25] In this study, 43% of patients received at least one off-label or unlicensed drug. The most common drugs prescribed off-label included terbutaline, ipratropium, ranitidine, paracetamol, senna, salmeterol, cephalexin and multivitamin drops. The most common unlicensed drugs were cyclizine injection, cisapride, clonazepam and morphine/ cyclizine injection. Off-label prescribing was predominantly due to a different dose prescribed than in the product license (52%), age (24%) and indication (24%).[25]

The extent of off-label prescribing in Italy involving non-specialised wards was reported to be higher. In a prospective study of 1461 children (aged one month to 14 years) admitted to the general paediatric wards of nine Italian hospitals during a 12 week period, involving 4265 prescriptions (of which 10 were excluded as they were unlicensed drugs), the average number of drugs per child was 2.9.[63] Only 0.2% of drugs were unlicensed but as the study concerned itself with off-label prescribing, these drugs, which included chloral hydrate, captopril, ceftriaxone, theophylline and fludrocortisone, were

excluded from the study. The reason for the low rate of unlicensed prescribing in this study was that only general paediatrics wards were involved rather than speciality/subspeciality wards, where unlicensed prescribing may be higher. The overall extent of off-label prescribing was 60% but differed between hospitals (range 44% to 71%). Some drugs e.g. cardiovascular drugs, had the highest rate of off-label use, with 100% of prescriptions off-label. The average proportion of paediatric patients receiving at least one off-label prescription was 81% but this was reported as high as 96% in one Italian hospital. The rate of off-label prescribing varied according to the underlying condition (i.e. it varied from a minimum of 46% for otitis media to a maximum of 100% for hypotension). The main reason for off-label prescribing was dosage. Drugs most commonly administered at higher doses than approved in the product license included beclomethasone, paracetamol and betamethasone.[63]

1.6.5 Emergency Departments

Studies have investigated the extent of off-label prescribing in hospital Emergency Departments. In the US, a 30 day retrospective chart review study involving children aged 4 days to 17 years investigated whether or not drugs were approved by the FDA for patient's age.[64] The study, which included 359 patients who received medication while in the Emergency Department, reported that 43% of patients received one or more drugs not approved for use at the patient's age. This study did not investigate compliance of dose, indication or route of administration. Children aged three to 11 years made up the highest proportion of non-approved drug use. Medication classes most commonly associated with off-label drug use were bronchodilators, benzodiazepines and narcotic analgesics.[64]

In a retrospective four year study of eight paediatric Emergency Departments in Italy that specifically investigated the off-label use of antiemetics in children with vomiting related to acute gastroenteritis, 30% of antiemetics were administered off-label (10% for indication and 20% for dose) to 19,879 patients aged zero to 17 years.[65] Ondansetron and metoclopramide were

used off-label for both age and indication in all Emergency Departments studied. The researchers reported that off-label prescribing was more common in children aged less than two years.[65]

1.6.6 Outpatients

Several studies have investigated the extent of off-label and unlicensed prescribing in the outpatient setting. The exposure of children to off-label and unlicensed medicines in outpatient settings is not as high as in NICUs (90% babies)[43] and in paediatric general ICUs (70%)[51] but since a large number of sick children are treated as outpatients (in ambulatory clinics), the problem is nevertheless significant. In a two month retrospective study in Israel, Gavrilov et al. reviewed the medical records of 132 outpatient children (aged one month to 18 years) which evaluated 222 medicine prescriptions for 63 different drugs.[66] They reported that 8% of prescriptions were unlicensed and 26% were off-label. The ten most commonly used off-label and unlicensed drugs were ferrous carbonate, thyroxine sodium, cisapride, salbutamol, clindamycin, amoxicillin trihydrate, budesonide, aluminium hydroxide/ magnesium hydroxide, amoxicillin trihydrate/ clavulanic acid and captopril. The most common categories of off-label medicine use were different dose and age. There were 42% of patients that received one or more off-label or unlicensed drugs. The researchers reported that many paediatric patients received medications that were not available in liquid form for oral administration and that the pharmacy department crushed tablets to make them suitable for children. However, bioavailability and stability data are often not available for those preparations.[66]

A six month retrospective study was conducted in the UK in a paediatric gastroenterology outpatient department and included children discharged home following an in-patient stay. This study involved prescription records of all paediatric outpatients under the care of three gastroenterologists, retrieved from a pharmacy database.[47] A total of 308 children (aged 20 days to 17 years, median age 8.1 years) received 777 prescriptions, referring to 69 different drugs for various chronic gastrointestinal diseases including irritable

bowel disease, malabsorption and gastroesophageal reflux. Of the 777 prescriptions, 49% were off-label (37.5%) or unlicensed (11.9%). Reasons for off-label prescribing included indication and age, with the majority off-label for indication. Off-label medications included domperidone, ranitidine, omeprazole, azathioprine, tacrolimus ointment, metronidazole, mesalazine, polyethylene glycol, paraffin oil and tripotassium dicitrobismuthate. Unlicensed medications included cisapride, omeprazole suspension, mercaptopurine liquid and glyceryl trinitrate ointment. The extent of unlicensed prescribing reported in this study highlighted that chronically ill children treated on an outpatient basis in sub-specialities such as paediatric gastroenterology are most likely to require the use of unlicensed medications in the community setting.[47]

Off-label prescribing was also common in the outpatient setting in Estonia. In a retrospective 12 month drug utilisation study based on the Estonian Health Insurance Fund prescription database on subjects aged below 19 years, Lass et al.[67] reported that of 467,334 prescriptions dispensed to 151,476 children, 31% were off-label and 0.05% were unlicensed. In this study, drugs were classified as off-label if there was a lack of paediatric information in the SPC (Summary of Product Characteristics), if the drug was contraindicated or if it was prescribed to a child below the lowest approved age. A drug was classified as unlicensed if the product had no official marketing authorisation in Estonia. A majority of off-label drugs did not have any information on paediatric use in the SPC. Anti-infectives were the most commonly prescribed group of drugs. This study did not report the percentage of patients that received off-label or unlicensed drugs.[67]

Several studies have investigated only off-label prescribing to outpatients. A retrospective study in the US by Bazzano et al.[68] collected data from 7901 outpatient visits by children (aged zero to 17 years) over a three year period from the National Ambulatory Medical Care Survey. Characteristics of an estimated 312 million visits, in which at least one medication was prescribed, were analysed. At 62% of prescription visits, at least one off-label prescription for age or indication was prescribed. Approximately 96% of

cardiovascular-renal, 86% of gastrointestinal and 67% of pulmonary and dermatological medication prescriptions were off-label. The five medications most commonly prescribed off-label were amoxicillin, albuterol (salbutamol), azithromycin, montelukast and amoxicillin/ clavulanic acid. Visits by children aged under six years had a higher probability of off-label prescribing ($p < 0.01$), especially visits by children aged less than one year and children who received more than one drug were also significantly more likely to receive off-label prescriptions.[68]

Similar findings for the extent of off-label prescribing in outpatients were reported in a recent study conducted in Spain.[48] A 10 month retrospective study in a paediatric gastroenterology outpatient clinic of a tertiary care university hospital included 609 patients (aged 22 days to 15.6 years) with the most common clinical diagnoses reported as gastroesophageal reflux disease, constipation, inflammatory bowel disease, *H. pylori* infection and intestinal malabsorption. Two hundred and seven patients received a total of 331 drug prescriptions, of which 33.2% were off-label. However, in children younger than two years, 85.5% of prescriptions were off-label. The most frequently prescribed off-label drugs were domperidone, ranitidine, omeprazole, azathioprine, tacrolimus, metronidazole, mesalazine and polyethylene glycol. The main reason for off-label prescribing was related to age. Up to 47.3% of patients received at least one medicine under off-label conditions.[48]

A retrospective 10 month study in Portugal in which data were obtained for 700 randomly selected children (aged four days to 18 years), from the Hospital Electronic Medical Records database reported similar trends in the percentage of off-label prescriptions to the study in Spain. In this study, 92 different drugs were prescribed on 724 occasions for 427 patients.[69] The study, which considered only the medicines prescribed to be used after discharge, reported that 32.2% were off-label. At least one drug was used off-label for 28.1% of the studied population, corresponding to 46.1% of the 427 patients. The five most commonly prescribed off-label drugs were amoxicillin/ clavulanic acid, paracetamol, amoxicillin, ibuprofen and

salbutamol and the most common reason for off-label prescribing was alteration in dose.[69]

1.7 Adverse drug reactions (ADRs)

In a meta-analysis in paediatric inpatients and outpatients the incidence of ADRs in hospitalised patients was reported as 9.53% and in outpatients as 1.46%. Polypharmacy was identified as a potential predictor of adverse events and researchers raised concerns about the risk of ADRs with off-label and unlicensed drug use.[70]

Several studies have analysed the potential association between off-label or unlicensed drug use in children and the risk of ADRs. The incidence of ADRs has been reported to range from 2.53 to 19.9% in prospective inpatient studies.[71]

In a 28 month prospective UK study at the Alder Hey Children's Hospital, ADRs were studied in 899 critically ill infants and children aged zero to 16 years.[72] Seventy six ADRs, involving 35 different drugs, were reported in 63 patients, with an overall incidence of 7%. The majority of ADRs were mild but 19 were moderately severe and 8 were severe. About one third of the 76 ADRs were associated with drugs used outside their product license for dose, indication or age and one (allopurinol injection) was used in an unlicensed manner. The most common drug reported to cause ADRs was midazolam; others included morphine, salbutamol, vecuronium, hydrocortisone and theophylline.[72]

In a prospective 13 week study by Turner et al. in the UK, involving 1046 patient admissions, ADRs were more commonly associated with the off-label and unlicensed use of morphine, other opiates and antihypertensives/ vasodilators.[23] The researchers reported that ADRs occurred more frequently in ICUs and were commonly associated with off-label or unlicensed drugs

(6%) compared to licensed drugs (3.9%). Of the nineteen drugs involved in severe ADRs, 14 were either off-label or unlicensed. Critically ill patients were more likely to suffer an ADR which may be because they are exposed to more drugs. Although the risk of an ADR was associated with the number of medications administered ($p < 0.0001$), there was no significant relationship between the use of off-label or unlicensed drugs and the risk of an ADR ($p < 0.106$).[23]

In an eight month prospective study in a 10-bed isolation ward at the University Hospital Erlangen-Nuremberg, Germany, involving 178 patients aged less than 18 years, 156 patients were prescribed drugs and monitored for ADRs.[50] The study included 740 prescriptions of which 198 were off-label or unlicensed. The percentage of ADRs in patients that were prescribed drugs was 19.9% and the incidence of ADRs increased significantly with the number of drugs prescribed ($p < 0.05$). Thirty-one patients reported a total of 46 ADRs. Of the 92 patients that were prescribed off-label or unlicensed drugs, 26 patients (28.3%) experienced an ADR whereas of the 64 patients prescribed only licensed drugs, five patients experienced an ADR (7.8%). The researchers reported that ADRs were associated with 6.1% of off-label or unlicensed drugs and 5.6% of licensed drug however differences between licensed and off-label/ unlicensed drugs were not significant.[50]

More recently, an increased risk of ADRs associated with off-label and unlicensed drug use was reported in a five month study in a paediatric public hospital ward in Brazil.[59] The prospective study, involving 272 patients aged zero to 16 years, of which 265 patients received at least one drug, reported that 82.6% of children received at least one off-label or unlicensed drug and 17% of children received both. The overall incidence of ADRs in the whole study population was 12.5%. In patients exposed to at least one off-label drug, the incidence of ADRs was 16.3%. Off-label drug use was significantly associated with ADRs (RR 2.44; 95% CI 2.12, 2.89). The more common ADRs associated with off-label use were skin eruptions.[59]

Evidence from retrospective studies is conflicting. In a retrospective study in Sweden investigating spontaneous ADRs involving drugs prescribed for outpatients younger than 16 years of age, researchers reported that 42.4% of ADRs were related to the use of drugs prescribed outside the terms of the product license.[73] This is in contrast to a more recent retrospective study in Denmark investigating spontaneous ADRs reports for children aged zero to 17 years, which reported that of 4388 ADRs analysed, 17% were associated with off-label use and of these, 60% were serious.[74]

ADRs for children are underreported and this may be even more common for off-label and unlicensed drugs. There is accumulating evidence of harm and an increased incidence of ADRs associated with off-label and unlicensed prescribing.[75] The proper evaluation of some drugs that have long established off-label uses has shown that they are either ineffective or harmful. For example, as a result the Paediatric Rule legislation in America, paediatric studies found a higher percentage of deaths were reported in patients who received propofol compared with controls in the paediatric ICU.[76]

1.8 Ethical issues in off-label and unlicensed prescribing

In Australia there is no legislation that requires drug companies to conduct paediatric studies. However, as the Quality Use of Medicines (QUM) is one of the central objectives of the NMP (defined as selecting management options wisely, choosing suitable medicines if a medicine is considered necessary and using medicines safely and effectively) the Medical Journal of Australia published some guidelines in 2006 as a practical and explicit approach to assist clinicians trying to make decisions about the appropriateness of off-label prescribing.[77]

Up to 90% of newborn children in ICUs are prescribed off-label or unlicensed drugs despite the lack of regulatory demonstrated efficacy, safety and toxicity

including ADRs. It is not illegal in most countries and may be appropriate in certain situations provided there is no alternative and the likely benefits outweigh the potential risks.[53, 71, 78] The main ethical issue is around safety and ADRs and relates to concerns about harm to the patient.

There are a number of barriers to conducting clinical trials in children to determine the safety and efficacy of drugs. Whereas research to improve child health is now considered an ethical obligation, previously there was an emphasis on the need to protect children against research.[79]

1.9 Barriers to developing medicines for paediatric patients

Drug manufacturers are reluctant to test drugs in children because of economic, ethical and legal reasons yet research to improve child health is now considered an ethical obligation.[80] The consensus to protect children against research has moved to a need of having reasonable evidence of both safety and efficacy of paediatric medicines. One of the main barriers to research on children's drug development is probably the limited commercial interest because the paediatric population is smaller and healthier than the adult population. Diseases in children are rarer and often of short duration therefore the market for pharmaceutical companies may be limited.[79] There is also a deficient infrastructure for conducting paediatric clinical trials and difficulties in trial design, including ethical difficulties. As paediatric age groups vary from preterm neonates to adolescents, they are not a homogenous group so the response to therapy varies with development, size and maturation of biochemical pathways. For proper research to be conducted there may be difficulties in predicting or determining the concentration-response or dose-response relationship. The different age ranges and the effects of growth and changing physiology on drug handling must be taken into consideration since these can affect health, even a long time after the drug has been administered, especially growth and sexual development.[78, 79] Further, formulations suitable for children, especially very

young children, may not be available and reformulating tablets or capsules from adult dosage forms may result in unknown pharmacokinetic consequences.[78, 79]

Similar barriers to marketing medicines and formulations suitable for use in children have been identified in Australia. A Paediatric Medicines - Industry Scoping Study which consulted 21 pharmaceutical companies of varying size and scope identified economic, regulatory, logistical, ethical and technical barriers.[81] In Australia, the size of the paediatric market is limited so there is a relative economic disincentive for manufacturers to commit resources to paediatric testing due to financial concerns relating to the cost/benefit ratios. Further, if pharmaceutical companies do not conform to government regulations, they will not be allowed to supply goods. The lack of paediatric research infrastructure and validated paediatric assessment tools poses additional challenges and recruiting paediatric patients may be a slow process when compared to recruiting adult patients. Technical barriers identified related to challenges of producing and administering medicines appropriate for children since adult formulations may not be suitable or not palatable for children.[81]

1.10 Regulatory aspects

1.10.1 United States perspective

It is only in recent years that regulatory authorities have devoted attention to the paediatric use of off-label or unlicensed dugs. Between 1973 to 1997 in the United States, around 71 to 81% of approved drugs contained no labelling information for children and despite lacking adequate data on efficacy, safety and appropriate dosing, many drugs were administered to children in an unapproved manner.[12, 82] The first FDA regulations on drug use in children were the introduction of a paediatric section in the package insert in 1979.[21] In 1994, the "Pediatric Rule" was introduced, which allowed adult safety and efficacy data to be extrapolated to children in certain cases where

the course of the disease and the drug's effect were sufficiently similar.[83] However, the results of these initiatives were not sufficient to adequately address the lack of paediatric information and other measures followed. In 1997, as part of the Food and Drug Administration Modernisation Act (FDAMA), a new law, known as the paediatric exclusivity provision, was enacted.[47, 84] This law provided an additional six months of marketing exclusivity in return for conducting paediatric studies.[76] In 1998 a mandate was added to the "Pediatric Final Rule" requiring paediatric drug testing for all new drug applications, including all new molecular entities and all supplemental indications for approved drugs.[12]

In 2002, the Best Pharmaceuticals for Children Act (BPCA) renewed the exclusivity provision and was extended through to 2007.[60] Although the incentive has been the driving force in stimulating paediatric research studies into both new and more established drugs, the "Pediatric Final Rule" was overturned by a federal court in 2002 on the grounds that the FDA did not have authority to mandate that paediatric drug studies are conducted by manufacturers. However, in 2003 the "Pediatric Research Equity Act (PREA)" was established via Congress and enforced the power of the FDA to require drug makers to conduct paediatric trials.[21] The paediatric research provisions have sometimes been referred to as "the carrot and the stick" with the BPCA offering the carrot - extending market exclusivity in return for specific studies on paediatric use - and the PREA providing a stick - requiring studies of a drug's safety and effectiveness when used by children.[80] Nevertheless, hundreds of drug trials have been conducted in children as a result of the US regulations that have provided information and new pharmacokinetic data and dosing instructions, safety data and critical new warnings.[85, 86] The PREA and BPCA have resulted in 335 written requests issued (1998 to July 2011), 323 marketing applications were approved with post marketing requirements (through May 2011) and 415 labels changed (1998 to July 2011).[87] In 2007, the Food and Drug Administration Amendments Act (FDAAA) amended and reauthorised the BPCA incentive and PREA authority until October 2012. The FDAAA also introduced the "Pediatric Review Committee (PeRC)", which includes FDA employees with

expertise in various areas including clinical pharmacology, paediatrics, paediatric ethics and legal issues, to provide the framework for the preparation of consultation on and general review of paediatric information to help ensure consistency and quality.[84]

1.10.2 European perspective

In Europe, the agency that evaluates medicinal products is the European Medicines Agency (EMA) which was formerly known as the European Agency for the Evaluation of Medicinal Products (EMEA) and established from 1995 to 2004. In 1997, the EMA created the "Note for guidance on clinical investigation of medicinal products in the paediatric population" describing how and when drugs should be tested in children.[21] As the note only contained guidelines, new legislation (Regulation [EC] No. 1901/2006 as amended) namely the "Paediatric Regulation" governing the development and authorisation of medicines for use in children aged zero to less than 18 years was introduced in the European Union in January 2007.[57] By establishing a framework of requirements, incentives, obligations and rewards for pharmaceutical companies similar to the PREA in the United States, the legislation aims to encourage the development of medicines appropriately tested, authorised and formulated for use in the paediatric population.[79, 88] As part of the "Paediatric Regulation", companies are required to submit a Paediatric Investigation Plan (PIP) to the Paediatric Committee (PDCO) of the EMA to reach agreement on proposed studies and measures to be undertaken for new medicinal products to provide data to enable the assessment of the quality, safety and efficacy in children and the benefit/risk profile in the paediatric population. The PDCO may grant a waiver from the obligation to undertake studies when medicinal products are expected to be unsafe or ineffective in children or where a particular medical condition does not occur in children.[79] Additionally, as off-patent medicines are of little commercial interest to pharmaceutical companies, the Paediatric Regulation includes provisions for funding studies into off-patent medicinal products. An updated list of priorities was agreed by the PDCO in August 2013.[89]

1.10.3 WHO Initiatives

Promoting safe and appropriate drugs for children is a global concern. In 2007, the World Health Organization (WHO) launched the 'Make medicines child size' campaign to raise awareness among health care professionals, pharmaceutical manufacturers, policy makers, researchers and the public. In the same year, the first WHO Model List of Essential Medicines for Children was released and identified medicines that should be available for use in children.[90] The list is updated every two years and the current list, the 4th WHO Essential Medicines List for Children, was updated in April 2013 and revised in October 2013.[91] In 2010, the first WHO Model Formulary for Children was released allowing medical practitioners worldwide to have access to standardised information on how to use over 240 essential medicines for treating illness and disease in children.[92]

1.10.4 Australian perspective

One of the aims of the Australian government is to have equal access to medications for all patients. However, in the 1990's, the Australian Drug Evaluation Committee found that there was a lack of access to medications for children so in 1995 the Working Party on the Registration of Drugs for Use in Children was established. Although several recommendations were made, the lack of incentives did not encourage their uptake.[3] In 1997, the Orphan Drug Program was established. The TGA defines an "orphan drug" as a medicine, vaccine or *in vivo* diagnostic agent that is intended to treat, prevent or diagnose a rare disease that is not commercially viable to supply to treat, prevent or diagnose another disease or condition.[93] Although the Orphan Drug Program was not specific to children, it aimed to encourage drug companies to provide essential products for rare conditions to Australia, while ensuring the same level of safety, efficacy and quality as other products and involved evaluation fees being waivered for drugs with small patient populations (< 2000). As the concerns around paediatric medicines continued, the Australian Health Minister's Advisory Council (AHMAC) set up a working party to consider issues relating to registration of paediatric

pharmaceuticals and appropriate access.[3] This led to the establishment of the Paediatric Medicines Advisory Group (PMAG) by the Department of Health and Ageing.[94] The PMAG has identified a priority list of medicines requiring access for paediatric use in Australia, which is reviewed and updated at each meeting.[3]

A list of priority drugs and their clinical need for consideration by the PMAG was prepared in one of the initial meetings in October 2007 (Table 1.1).[95] As a result of the work by the PMAG, by 2008, clarithromycin powder and levetiracetam were listed on the Pharmaceutical Benefits Scheme (PBS).[96] In an outcome statement in June 2012, the PMAG reported that as a result of its work, a number of new medicines had been listed on the PBS including arthemether with lumefantrine dispersible tablet, clarithromycin powder for oral liquid, cefuroxime oral suspension, fluconazole powder for oral suspension, lansoprazole tablet (orally disintegrating), levetiracetam oral solution, ondansetron syrup, tocilizumab concentrate for injection and voriconazole powder for oral suspension. Access to diazoxide oral suspension via the Special Access Scheme had improved as a result of the PMAG's work and there had also been several amended listings on the PBS, including risperidone oral solution, methylphenidate hydrochloride, ciprofloxacin ear drops, dornase alfa solution for inhalation, albendazole chewable tablets, nevirapine oral suspension, terbinafine, deferasirox dispersible tablet, ribavirin with pegylated interferon and atenolol 50mg/10mL oral liquid.[97] The PMAG continues to liaise with expert paediatric groups and pharmaceutical companies to discuss medications on the PMAG's priority list. The most recent list, as at October 2012, is shown in Table 1.2.[98]

Table 1.1 - Medicines under PMAG consideration as at October 2007.[95]

Medicine	Clinical Need as agreed by the PMAG
aciclovir suspension	to treat herpes simplex infections/ prevent recurrent attacks of herpes simples infections
atenolol solution	beta-blocker used to treat hypertension and angina
calciferol/ cholecalciferol	vitamin D deficiency
calcitriol drops	renal bone disease
ciprofloxacin suspension	cystic fibrosis, atypical mycobacterial infections and urinary tract infections
clarithromycin powder	pertussis and atypical mycobacterial infections, particularly immunosuppressed patients
clindamycin suspension	Community acquired MRSA and osteomyelitis
diclofenac dispersible tablets	NSAID used to treat pain and inflammation
flecainide solution	used to treat cardiac arrhythmias
fusidic acid suspension	anti-infective used to treat MRSA
gabapentin suspension	used for neuropathic pain and as anticonvulsant
melatonin tablets	sleep disorders
midazolam oral suspension	sedative
nitrofurantoin suspension	antibiotic for prophylaxis and treatment of complicated urinary tract infections
spironolactone suspension	congenital heart disease in neonates and chronic lung disease
trimethoprim suspension	antibiotic for prophylaxis and treatment of complicated urinary tract infections

Another priority of the PMAG was the development of a national paediatric prescribing manual. This was achieved with support from the AHMAC, as part of the Paediatric Pharmaceuticals Prescribing Resource Project and led to the publication of the Australian Medicines Handbook (AMH) Children's Dosing Companion in 2013.[99] The resource provides detailed dosing information for around 230 drugs and will be updated with more drugs every six months. Dosages are provided by indications and/or age groupings from toddlers to teens. Other specific information relating to each drug's paediatric use is included, as well as off-label use and all content is evidence-based and peer reviewed. Further, the Australian Medicines Handbook Children's Dosing Companion[99] makes reference to the proposed framework published in the Australian Medical Journal in 2006 as a guide for clinicians and others for the off-label use of medicines.[77] According to the article, off-label prescribing may be considered appropriate if there is high-quality evidence supporting its use, within formal research or in exceptional use in an individual patient (e.g. if there is a serious underlying disease or condition).[77]

The recent initiatives in Australia with the availability of an evidence-based and peer reviewed paediatric prescribing information resource, the guidelines published in the Medical Journal of Australia and the PMAG national decision-making framework have led to some improvements in the use and access to children's medicines.[77] However, despite strong professional advocacy on many fronts, there is still a lack of any legislative and regulatory reforms addressing paediatric medicines.[78, 85] Unlike the United States and Europe, there is currently no specific government commitment to give high priority to paediatric medicines issues.[85]

Table 1.2 - Medicines under PMAG consideration as at October 2012.[98]

Medicine	Clinical Need as agreed by the PMAG
abatacept	polyarticular juvenile idiopathic arthritis
adalimumab	uveitis related to juvenile idiopathic arthritis, enthesitis and Crohn disease
anakinra	systemic juvenile idiopathic arthritis
bosentan	pulmonary hypertension
calciferol/ cholecalciferol	vitamin D deficiency
clindamycin suspension	Community acquired MRSA and osteomyelitis
clobazam tablets	resistant epilepsy
diazepam mixture	chronic spasticity
glycopyrrolate oral solution	drooling
infliximab	ankylosing spondylitis
Kindergen®	medicinal food for older children
leflunomide	juvenile idiopathic arthritis
leuprorelin	precocious puberty
melatonin	sleep disorders particularly those with neurological impairment/ cortical blindness
mycophenolate sodium	nephrotic syndrome
natalizumab	refractory multiple sclerosis
6-mercaptopurine/ thioguanine suspension	acute leukaemia
tacrolimus suspension	organ transplant
triamcinolone hexacetonide	steroid joint injections for juvenile idiopathic arthritis

1.11 Lincomycin

An example of a drug used off-label in children is lincomycin. The safety and effectiveness in paediatric patients below the age of one month has not been established. Lincomycin injection also contains the preservative benzyl alcohol which has caused fatal gasping syndrome in premature infants.[30] The use of lincomycin reconstituted with various intravenous fluids is considered unlicensed since this formulation is unlicensed and current use is non-evidence based in that there are no data on the stability of these formulations.

1.11.1 Antimicrobial activity and indications

Lincomycin, a naturally occurring lincosamide antibiotic obtained as a fermentation product of *Streptomyces lincolnensis var lincolnensis* binds to the 50S subunit of bacterial ribosomes to suppress protein synthesis.[100] Its action may be bactericidal or bacteriostatic depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism.[101] It has a spectrum of activity against Gram positive bacteria and most anaerobes, but not Gram negative aerobes.[100] It is indicated for the treatment of serious infections due to susceptible strains of staphylococci, streptococci and pneumococci and is generally reserved for patients who are allergic to penicillin.[30] Specific indications for lincomycin include upper and lower respiratory tract infections, skin and skin structure infections such as cellulitis and abscesses, septicaemia, endocarditis, bone and joint infections, including osteomyelitis and septic arthritis.[30] At PMH, in paediatrics, it is frequently used to treat surgical and medical paediatric patients with or at risk of non-multiresistant staphylococcal infections or those with complicated pneumonia and empyemas. It is also used in those allergic to a beta-lactam antibiotic that require empiric gram positive cover, e.g. intra-abdominal sepsis, pneumonia.[100]

1.11.2 Chemistry

The chemical name of lincomycin is methyl 6-amino-6,8-dideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-α-D-*erythro*-D-*galacto*-octopyranoside.[102] It serves as a starting material for the synthesis of clindamycin, which is a semisynthetic derivative of lincomycin with a closely related structure (Figure 1.1).[100] The spectrum of activity of lincomycin resembles that of clindamcyin, although lincomycin is generally less active against susceptible organisms than is clindamycin. There is complete cross-resistance between the two antibiotics. Partial cross-resistance has also been reported between lincomycin and macrolides (erythromycin).[101]

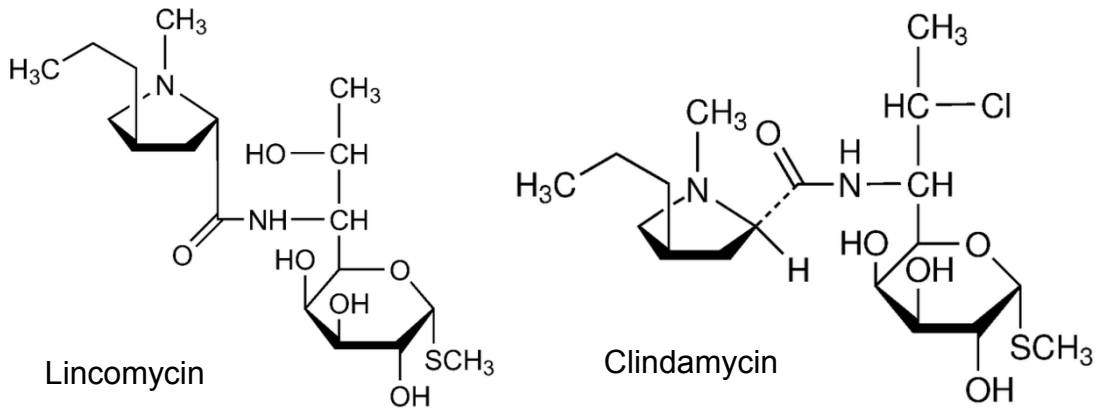


Figure 1-1 - Structure of lincomycin and clindamycin.[102]

Lincomycin is a basic compound in which the single amine group is tertiary with a pK_a of 7.6. The free base is soluble in water and most organic solvents other than the hydrocarbons. The crystalline hydrochloride salt, which is freely soluble in water, soluble in dimethylformamide and very slightly soluble in acetone, forms hydrates.[30, 103] Lincomycin hydrochloride monohydrate is a very stable white or almost white, crystalline powder that is odourless or has a faint mercaptan-like odour and a bitter taste.[100, 104] Its molecular weight is 461.0g. A 10% solution in water has an acid pH between 3.0 and 5.5 therefore incompatibility may be expected with alkaline preparations or with drugs unstable at low pH.[102]

1.11.3 Pharmacokinetics

Lincomycin is administered orally or parenterally as the hydrochloride. Doses are expressed as the base with 1.13g of lincomycin hydrochloride equivalent to about one gram of lincomycin.[102] The usual adult oral dose is 500 mg three to four times daily. Lincomycin is rapidly but only partially absorbed from the gastrointestinal tract and an oral 500 mg dose of lincomycin hydrochloride reaches peak serum levels of two to three microgram/mL in two to four hours and decreases to one microgram/mL in a further four to eight hours. Total absorption and peak serum levels are significantly reduced by food.[30, 100] In Australia, lincomycin is not available as oral dosage forms and is administered parenterally by intramuscular injection in a dose of 600 mg every 12 to 24 hours, or by slow intravenous infusion in a dose of 600 mg to one gram every eight to 12 hours.[30] The dose for children over one month of age depends on the severity of infection and 10 to 20 mg/kg/day may be infused in divided doses.[30, 102]

Lincomycin is widely distributed in a volume approximating to the total body water.[100] It reaches insignificant cerebrospinal fluid levels in persons with normal meninges and attains concentrations that are approximately 40% of those in the blood in cases of meningitis.

A substantial proportion of lincomycin is inactivated in the body, presumably in the liver. Bile is an important route of excretion.[30] About 40% of an oral dose can be recovered from faeces. Less than 5% of an oral dose appears in the urine over 24 hours, but up to 60% after intravenous administration, mostly in the first four hours.[100] The biological half-life of lincomycin after oral, intramuscular or intravenous administration is 5.4 $\pm$ 1.0 hours.[30] In patients with severe hepatic dysfunction, the plasma half-life is approximately doubled.[100]

1.11.4 Availability in Australia

Lincomycin and clindamycin are both available in Australia as solutions for injection but only lincomycin injection (600 mg in 2 mL) is available on the PBS.

In a discussion with the Chief Pharmacist and Head of Department of Microbiology at PMH, they advised that there was a lack of adequate data on the stability of lincomycin in systems used by the hospital. Lincomycin injections are extemporaneously prepared so they are currently considered unlicensed and there is, at the moment, no stability data available.

This thesis aimed to determine the stability of lincomycin in commonly used IV fluids, including 0.9% sodium chloride, Hartman's solution, 5% glucose solution and 10% glucose solution. To achieve this, an appropriate analytical technique using a reverse phase high performance liquid chromatography (HPLC) - mass spectrometry assay based on a method by Catena et al.[105] was developed.

1.11.5 Stability studies

Few studies on the stability of lincomycin seem to be available in the literature although a study published in 1965 reported on the acid stability of lincomycin at 37°C and 70°C to predict the stability of lincomycin in the stomach following oral administration.[106] Solutions containing 0.4% lincomycin hydrochloride with 0.1 M HCl were incubated and samples analysed at specific time intervals. Lincomycin hydrochloride in 0.1 M HCl at 37°C showed no degradation for at least 48 hours and at 70°C, it degraded slowly with a half-life of 39 hours.[106]

Importantly, when lincomycin is administered intravenously, doses are administered on the basis of 1g Lincocin® diluted in not less than 100 mL of an appropriate solution and infused over a period of not less than one hour. Administration at greater than the recommended concentrations and rate has

resulted in severe cardiopulmonary reactions.[30] Infusion solutions stated in MIMS to be physically compatible with Lincocin® include glucose 5% intravenous infusion, glucose 10% intravenous infusion, sodium chloride 0.9% and glucose 5% intravenous infusion, sodium chloride 0.9% and glucose 10% intravenous infusion, compound sodium lactate intravenous infusion, sodium lactate 1/6 molar and Dextran 70 intravenous infusion.[30] However, according to MIMS "compatibility determinations of lincomycin in these IV fluids are physical observations only and not chemical determinations. Adequate clinical evaluation of the safety and efficacy of these combinations has not been performed".[30]

As previously mentioned, intravenous administration of Lincocin® requires dilution of the 2 mL ampoule in an appropriate solution. This produces an unlicensed product. There is currently no mechanism for inclusion of such products in the product information (PI) to render the formulations as licensed, therefore giving rise to formulation uncertainty. The next best option is to provide scientific information on the compatibility and stability of such formulations which goes part of the way to facilitating their clinical use. Already lincomycin hydrochloride is reported in the American Hospital Formulary Service (2014)[101] to be physically compatible for 24 hours at room temperature in commonly used intravenous fluids. However, there may be instances where prolonged storage of lincomycin in IV solution is required.[101] For example, in case of rural administration, several days supply of lincomycin in IV solutions may be needed or in the 'hospital in the home' setting, it may be necessary to store lincomycin in IV solution for several days. For these reasons, it was decided to investigate the stability of lincomycin in different IV solutions over 31 days in order to determine its potential stability.

Chapter 2

Materials and Methods

Part 1
Off-label and unlicensed prescribing

2.1 Patients

Medical records from Princess Margaret Hospital (PMH) from a population of 145,550 patients seen at the hospital between 1st January 2008 and 31st December 2008 were sampled to obtain a random selection of 1200 records from Emergency Department admission, inpatients and outpatients. These were obtained from 55,591 records of Emergency Department admissions, 24,425 records from inpatient admissions and 65,534 records from outpatient encounters. The ratio of Emergency Department patients to inpatients to outpatients were maintained to generate a randomly selected list of 1200 cases. For the Emergency Department cases, the 55,991 patients were arrayed in Excel. Using a Randomisation process, they were randomly unsorted and the first 458 displaying cases copied and pasted to a new Excel sheet. The process was repeated for inpatients and outpatients to obtain the first 202 displaying inpatient cases and the first 458 outpatient cases respectively. In the new Excel spreadsheet, the 1200 cases were scrambled across the three groups from which to draw subjects and an event date in 2008 was recorded for each record. Of the 1200 records, data from 1038 records were collected. The reason for collecting data from this number of records was to give a precision of at least 2% for major findings. Each record had a unique identifying number that was kept by the Chief Pharmacist at PMH in case it was necessary to go back to any record for clarification of the data collected.

2.2 Ethics

A submission for approval of the project was made to the PMH Ethics Committee and the research was reviewed and approved by the relevant Hospital Quality Improvement Committee and also by the Executive Director for Medical Services in accordance with the National Statement 2007 (Audit

103QP - Prescription of off-label or unregistered medications - GEKO 1944) (Appendix 2). Human ethics approval was also obtained from the Human Research Ethics Committee at Curtin University, approval number PH-13-11 (Appendix 3).

2.3 Data collection

A data collection form was designed and optimised during a pilot phase of the study to collect the following data from each medical record: ID number, type of patient (inpatient, outpatient or emergency), sex, date of birth, weight, height, diagnosis, adverse effects, past medical history, ceased medications and reasons for ceasing. Prescribing details of all prescription medications were also collected including date of prescription, dosage form, dose, strength and frequency of administration. Prescription medications were defined as any medication written onto the patient's medication chart. Data were entered into a Predictive Analytics SoftWare (PASW) version 19 spreadsheet (a version of Statistical Package for the Social Sciences (SPSS)) for analysis.

2.4 Classification of data

2.4.1 Definition of off-label and unlicensed

Following data collection, all prescribed drugs were classified as registered, unregistered, off-label or unlicensed according to the 2008 Product Information (PI) available from the Therapeutics Goods Administration (TGA) website[107] or the Monthly Index of Medical Specialties (eMIMS).[108] Drugs were considered as registered if a PI for the drug was listed on the TGA website or in eMIMS. Drugs were considered unregistered (unlicensed) if no PI was available.

A comparison was made between the PI on the TGA website[107] or eMIMS[108] to determine whether prescribed drugs were licensed, unlicensed or off-label. Several categories of off-label prescribing were defined according to Turner:

1) Age/ weight - administration of a prescription drug outside the age range or weight for which the product is licensed.
2) Indication - the use for indications not described in the PI.
3) Route of administration - the use of alternative routes of administration other than the approved route for that formulation in the PI.
4) Dosage including dose frequency - the use of doses or dose frequencies other than those stated in the approved PI.

A prescription drug was considered off-label if it met at least one of the above four criteria according to the TGA or eMIMS PI.[107, 108] If there was any doubt as to whether a drug was off-label or not, to err on the side of caution, the drug was labelled as licensed. The same applied for uncertainty around unlicensed drugs.

The hierarchical approach adopted by Hsien et al.[42] was followed in this study. According to Hsien et al.[42], an off-label prescribed drug cannot be classified into more than one classification. Therefore, in keeping with Hsien et al. all prescriptions were initially analysed for age so that drugs with no paediatric information or those prescribed in an age group for which the drug was not licensed were classified as off-label for age. [42] In keeping with Hsien et al., the next hierarchical level was indication, then route of administration and finally dosage (which included frequency of administration). Where the TGA[107] or eMIMS[108] PI provided a drug dose range (e.g. Painstop® 1-2 yrs [10-12kg]: 5-6 mL), dosages administered outside this dose range were considered off-label. However, where the dose provided in the TGA[107] or eMIMS[108] PI was prescribed on a weight basis e.g. paracetamol 15mg/ kg/ dose, a variation of ± 10% was accepted to allow for practical dosage volumes.

Data entry was made into the PASW spreadsheet. Prescribed drugs that were off-label for age plus one or more other reasons were classified as off-label for age as this was considered the most important off-label classification. This was then followed by indication, then route of administration and finally dosage so that all PASW entries showed only the hierarchical off-label classification.

Where a PI was available for a drug but did not include a dose for children, the drug was classified as off-label, regardless of whether it was reformulated or not. For example, a dose was not included in the PI for carbimazole so it was classified off-label.[30, 107, 108] However, it was also reformulated to a suitable dosage form for a two month old child as no commercial liquid formulation was available. One exception was domperidone, which did not include a dose for children in the PI.[107] However the PI stated that extrapyramidal reactions occur rarely in young children which was suggestive that it could be used in children despite the absence of a dose in the PI. As domperidone was reformulated, it was classified as unlicensed.

A prescription drug was considered unlicensed if it was an unregistered drug, an unlicensed formulation of a registered drug, if a non-pharmacological substance was prescribed as a medicine or if the drug was obtained through the SAS, including drugs awaiting approval in Australia or those registered in another country. Unlicensed drugs included drugs that were not available in a paediatric formulation and required modification to either make the drug easier to be administered or to obtain a suitable dose size for administration to a child.

For all drugs that were reformulated, where the PI was available, this was consulted prior to classifying the drug. Some drugs were off-label for indication or age and were also reformulated (hence potentially classifying them as unlicensed). In these cases, if the PI stated that safety in children had not been established or that the drug was not recommended in children, then despite being reformulated, the drug was classified as off-label for purposes of data entry into the PASW spreadsheet. For other drugs, if a

commercially available product such as a tablet or an injectable product was reformulated, providing a dose for children was listed in the PI, the drug was classified as unlicensed. For example, propranolol is commercially available as 10mg, 40mg and 160mg tablets. In one case in this study, a 1 year old child was administered 2mg three times daily. The PI in eMIMS provides a children's dose (as 0.25 - 0.5 mg/kg) therefore the drug was not classified as off-label. However, to achieve a dose of 2mg, PMH prepared a liquid formulation which was not registered and not licensed, hence the drug was classified as unlicensed overall.

2.4.2 Patient classification

In analysing the outpatient data, it was found that for 52 patients all of their prescribing related to their 2008 inpatient record hence these have been recorded as inpatients for this study. None of their current medications had been prescribed as an outpatient.

2.4.3 Anatomical Therapeutic Chemical (ATC) classification system

Prescribed drugs were classified according to the organ or system on which they act and their pharmacological, therapeutic and chemical properties as defined by the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system.[109] Each drug was broadly classified into one of the following 14 groups:

A Alimentary tract and metabolism
B Blood and blood forming organs
C Cardiovascular system
D Dermatologicals
G Genito-urinary system and sex hormones
H Systemic hormonal preparations, excluding sex hormones and insulins
J Anti-infectives for systemic use
L Antineoplastics and immunomodulating agents

M Musculo-skeletal system
N Nervous system
P Antiparasitic products, insecticides and repellents
R Respiratory system
S Sensory organs
V Various

2.5 Pilot study

Prior to commencement of data collection from the 1038 medical records, a pilot study was conducted. The data collection form was used to collect data on 20 medical records that were unrelated to this study. The reason for the pilot study was to make any required modifications to the data collection form to ensure optimisation of data collection. Data collected from the pilot medical records were not included in this study as the data collected were not from 2008.

2.6 Preliminary analysis

A preliminary analysis of data from the first 200 medical records from the randomised 1200 records was conducted to ensure that the original assumptions were still relevant to the cohort. Each medical record was assigned an event date in 2008 and the data collected were from that specified event date. If the event was for ongoing care, for example a patient reviewed as an outpatient following treatment of a fracture on a previous occasion in 2008, then data were also collected for the previous event. However, if a previous (but related event) occurred in 2007, then these data were not collected. Each drug prescribed was classified into its appropriate ATC classification.

Where the same drug was prescribed to a patient but in a different dosage form (e.g. injection and oral dosage form) these were counted as two

separate drugs as this would have required two separate prescriptions to be written.

2.7 Age classification

All cases were classified according to the European Medicine Agency (EMA) age classification of paediatric patients:[6]

- Preterm newborn infants.
- Term newborn infants (0 to 27 days) - these have been termed neonates in this thesis.
- Infants and toddlers (28 days to 23 months) - these have been termed infants in this thesis.
- Children (2 to 11 years).
- Adolescents (12 to 18 years).

There were no preterm newborn infants included in this study as they are treated at another (maternity) hospital.

2.8 Exclusion criteria

Not included in this study were oxygen therapy, standard intravenous (IV) replacement solutions, blood products, flushes of NaCl 0.9% or heparin used to maintain patency of intravenous (IV) lines and TPN. Anyone aged 19 years or older was excluded from the study.

Since this was a retrospective study, for any cases where there was an uncertainty as to whether a drug was off-label or unlicensed (for example, if it could not be determined whether the drug had been reformulated), then the drug was classified as licensed.

Although a diagnosis for each patient was available in all medication charts, the indications for use of some drugs were not always clear. For example, several different dosage forms of ondansetron have TGA marketing approval including injections, tablets, wafers, syrup and suppositories. Ondansetron injections, tablets, wafers or syrup are licensed for children over four years of age for treatment of emetogenic chemotherapy or radiotherapy. However, ondansetron injection only is licensed for children aged two to 12 years of age for prevention and treatment of post operative nausea and vomiting (PONV). Several children of various ages were prescribed ondansetron wafers or syrup. Where there was no evidence that a child over four years of age prescribed ondansetron wafers or syrup was undergoing chemotherapy or radiotherapy, it was assumed the drug was prescribed for PONV and classified as off-label for indication.

2.9 Analysis of data and statistical evaluation

All data were entered into PASW for analysis. The appropriateness of prescribing for each drug was classified based on diagnosis, drug and dosage schedules and the drug's registration status with the TGA, including whether it was registered, registered for the indication and route of administration, registered for the age group and whether the dosage form prescribed was registered. The use of each drug ('status of prescribing') was classified as licensed, off-label, and unlicensed according to these various criteria.

Simple descriptive statistics were used to summarise the demographic data of the patients being studied (frequencies and percentages for categorical variables, means, standard deviations and ranges for variables measured on a continuous scale). The data were collected for each patient from medical records and included gender, age, type of patient (inpatient, outpatient or Emergency Department patient) and the number of drugs prescribed. Univariate differences between the proportions of patients prescribed licensed, off-label and unlicensed drugs for groups defined by the

demographic data (gender, age group, ward, etc) were compared using Pearson's chi-squared test (‘person-based’ comparisons). In addition the proportions of drugs classified as licensed, off-label and unlicensed in different drug classes (ATC codes), and patient demographic profile was evaluated in a similar manner (‘drug-based’ comparisons). The drugs most commonly prescribed off-label and unlicensed were tabulated. A p-value of 0.05 or less was taken to indicate a statistically significant association in all tests.

Linear regression analysis was used to determine the range of drugs prescribed and to look for variations in terms of age, diagnosis and gender. Data were analysed for appropriate prescribing and registration status. In addition the status of prescribing within specific drug classes and age groups was evaluated using PASW.

The results from the classification of prescribed drugs into off-label and unlicensed categories were used to determine the extent of off-label and unlicensed prescribing. The extent of off-label and unlicensed prescribing in each ATC category was determined and drugs most commonly prescribed off-label or unlicensed were identified.

Part 2
Lincomycin stability testing

2.10 Materials

2.10.1 Product investigated

The product investigated for this research was Lincocin® injection containing lincomycin hydrochloride 150 mg/mL and benzyl alcohol 9.45 mg/mL.

- Batch number F04815, expiry Oct 2013, Pfizer, Australia.
- Batch number G47185, expiry Nov 2013, Pfizer, Australia.
- Batch number G70495, expiry Sep 2014, Pfizer, Australia.

2.10.2 Standard

Pure analytical grade lincomycin hydrochloride monohydrate, Vetranal™ analytical standard, expiry 24 Nov 2014, Lot SZB8329XV, Fluka, Germany.

2.10.3 Materials used for buffer solutions

1. Acetic acid glacial, Univar AR, Ajax Chemicals N.S.W., Australia
2. Hydrochloric acid 1 M, freshly prepared.
3. Orthophosphoric acid 85%, Batch number 10173, Analar Grade, Australia.
4. Citric acid anhydrous BP. Batch number 4184E2, Ramprie, Australia
5. Sodium chloride analytical reagent, Batch number 04090105, Lab-Scan Analytical Sciences, Thailand.
6. Sodium hydroxide, Batch number 09G300017, Analar Normapur, VWR BDH Prolabo, Belgium.

2.10.4 Materials used for IV fluids

1. 0.9% Sodium chloride, Batch number S58R4, Expiry Jun 2015, Baxter, Australia.
2. Glucose monohydrate 5%, Batch number 12186410, Expiry Apr 2015, B. Braun Pty Ltd, Australia
3. Glucose monohydrate 10%, Batch number 14DC7301, Expiry Mar 2015, Fresenius Kabi, Germany.
3. Sodium lactate (Hartmann's solution), Batch number 122358143, Expiry May 2015, B. Braun Pty Ltd, Australia

2.10.5 Materials used for HPLC mobile phase

1. Acetonitrile, Batch number Lot123662, Fisher Scientific, U.S.A.
2. 50 mM orthophosphoric acid 85%, Batch number 10173, Analar Grade, Australia.
3. Sodium hydroxide, Batch number 09G300017, Analar Normapur, VWR BDH Prolabo, Belgium.

2.10.6 Materials used for stability indicating evaluations

1. Hydrogen peroxide 30%, Analytical Univar reagent, Batch number AF412330, Ajax Finechem, Australia.
2. Hydrochloric acid, Analytical Reagent Grade (32% hydrochloric acid), Batch number 1074496, Fisher Scientific, Loughborough, UK.
3. Sodium hydroxide, Batch number 09G300017, Analar Normapur, VWR BDH Prolabo, Belgium.

2.10.7 Water

Water was obtained from a Milli-Q Ultrapure water system, Millipore, Australia consisting of a 4-bowl ultrapure cartridge kit with conductivity of 0.05 μS.

2.11 Chromatographic equipment

2.11.1 HPLC

The High Performance Liquid Chromatography apparatus (HPLC) consisted of a Waters 501 HPLC Pump (USA) connected to a Rheodyne Model 7125 (USA) syringe loading sample injector with 20 μL sample loop, an ultraviolet detector (Waters 484, Tunable Absorbance Detector, Millipore, USA) and a Hewlett-Packard HP 3396 Series II integrator/ printer. Peak area was recorded as a measure of concentration and each unit of area was equivalent to 1/8 μV second. A Prosphere (150 mm x 4.6 mm, particle size 5 μ) and Apollo C18 (150 mm x 4.6 mm, particle size 5 μ) reverse phase HPLC column were used in conjunction with a reverse phase guard column as the stationary phase.

2.11.2 Water bath

- For temperatures of 25°C, a HetoFrig water bath, no 93082469 (Denmark), with a variable temperature of -40°C to 30°C and variability of ± 0.1°C, was used.
- For temperatures of 60°C and 80°C, a Grant water bath model JB1 (Cambridge), with variable temperature selection of 20°C to 90°C and variability of ± 0.1°C, was used

2.11.3 Thermometer

Zeal thermometer, 76 mm immersion, (England) was used as to monitor the temperature in the water bath.

2.11.4 pH meter

Hanna Instruments pH meter, model HI8519N (Singapore) which was calibrated with standard buffer solutions according to Section 2.11.5.

2.11.5 Standard buffer solutions

1. pH 4 (± 0.02 @ 25°C), Date of manufacture 0708, Batch number GA1339, BioLab Australia Ltd.
2. pH 7.00 (± 0.02 @ 25°C), Date of manufacture 0209, Batch number Lot GH1799, Hurst Scientific Pty Ltd, Armadale, WA

2.12 Assay methods

2.12.1 Assay for lincomycin HPLC optimisation

Lincocin® (lincomycin hydrochloride) (1 mL) was diluted to 100 mL with milliQ water and assayed by reverse phase HPLC to determine optimum conditions for the assay. The mobile phase used was a mixture of acetonitrile, 50 mM phosphoric acid and water, adjusted to pH 3.00 with 5 M sodium hydroxide. The mobile phase was filtered through a Millipore 0.45 μm filter. The percentage of acetonitrile for use with an Apollo column ranged from 5% to 40% and for a Prosphere column it ranged from 5% to 15%. The detection wavelength was 220 nm, the injection volume 20 μL and the flow rate 1.5 mL/min. All operations were carried out under ambient conditions. Possible conditions were informed by an assay for clindamycin.[105]

2.12.2 Assay validation

A stock solution of 1.0 mg/mL lincomycin hydrochloride was prepared by diluting 0.333 mL (measured with a micropipette) of Lincocin® to 100 mL with milliQ water. From this, standard solutions of 0.1 mg/mL to 1.0 mg/mL were freshly prepared and analysed by HPLC. The mobile phase consisted of 8% acetonitrile, 92% water, 50 mM phosphoric acid, adjusted to pH 3.00. A flow rate of 1.5 mL/min and wavelength of 220 nm were used. A calibration curve was produced by plotting the peak area under the curve (which

quantitatively represents the concentration of lincomycin in the sample) against the concentration of the samples.

Pure analytical grade lincomycin hydrochloride monohydrate was used to produce a 1 mg/mL stock solution in milliQ water. From this, standard solutions of 0.1 to 0.8 mg/mL were freshly prepared and analysed by HPLC to validate the reverse phase HPLC method and to determine the amount of lincomycin in a freshly prepared 0.6 mg/mL lincomycin hydrochloride sample using the Lincocin® injection.

Inter-day (repeatability) precision of a 0.6 mg/mL stock solution of lincomycin hydrochloride (prepared from Lincocin®) was determined using six replicate samples of stock solution for HPLC analysis. An intra-day (i.e. reproducibility) precision assay was determined by comparing the assay of 0.6 mg/mL lincomycin hydrochloride on two consecutive days. The results were expressed as the relative standard deviation (RSD).

2.12.3 Initial stability indicating assay

A 6 mg/mL lincomycin hydrochloride stock solution was prepared in 0.1 M HCl or 0.1 M NaOH respectively. From this, 5 x 5 mL solutions in 10 mL volumetric flasks were prepared and placed into a Grant Water bath model JB1 (Cambridge) at 60°C (± 0.1°C). These 5 mL samples were removed from the water bath at set time intervals (baseline, 4 hours, 6 hours, 7 hours and 24 hours for acid solution; baseline, 2 hours, 4 hours, 6 hours and 24 hours for base solution). Each 5 mL sample was neutralised with 0.5 mL of 1 M NaOH for acid solutions or 0.5 mL of 1 M HCl for base solutions, made to 10 mL with milliQ water and cooled to room temperature prior to HPLC analysis. The mobile phase consisted of 12% acetonitrile, 88% water and was adjusted to pH 3 with 50 mM phosphoric acid. A flow rate of 1.5 mL/min and wavelength of 220 nm were used.

2.12.4 Further stability indicating assays

The stability of lincomycin was tested in 0.1 M HCl, 0.1 M NaOH and 3% hydrogen peroxide. Stock solutions of 0.6 mg/mL lincomycin hydrochloride were prepared by measuring 0.4 mL of Lincocin®, adding 20 mL of 1 M HCl or 1 M NaOH respectively, and immediately making to 200 mL volume with milliQ water to produce 0.1 M HCl and 0.1 M NaOH solutions respectively. A stock solution of 0.6 mg/mL lincomycin hydrochloride in 3% hydrogen peroxide was prepared by making 0.4 mL Lincocin® up to 200 mL with 3 % hydrogen peroxide (prepared from 20 mL 30% hydrogen peroxide made to 200 mL with milliQ water). All solutions were placed into a Grant Water bath model JB1 (Cambridge) at 60°C and 5 mL samples removed at time zero and twice daily thereafter over a 7 day period. Each 5 mL sample of lincomycin hydrochloride in acid or base was neutralised with 0.5 mL of 1 M NaOH or 0.5 mL of 1 M HCl respectively and made to 10 mL with milliQ water. Samples of 5 mL lincomycin hydrochloride in hydrogen peroxide were made to 10 mL with milliQ water. Samples were cooled to room temperature prior to HPLC analysis. The mobile phase, flow rate and wavelength outlined in Section 2.12.3 were used.

2.12.5 Optimisation for resolution of lincomycin break down products

To optimise the resolution of lincomycin breakdown products, a stock solution of 0.6 mg/mL lincomycin hydrochloride was prepared by measuring 0.4 mL of Lincocin®, adding 20 mL of 1 M HCl, and immediately making to 200 mL volume with milliQ water. The solution was placed into a Grant Water bath model JB1 (Cambridge) at 60°C and 5 mL samples removed at time zero and every day thereafter for an 18 day period for HPLC analysis. Each 5 mL sample was neutralised with 0.5 mL of 1 M NaOH, made to 10 mL with milliQ water and cooled to room temperature prior to HPLC analysis. The initial assays were performed using the same conditions as outlined in Section 2.12.3. The effect of reducing the flow rate to 1.0 mL/ min was tested for a single run on day 14. On day 18, the effect of changing the mobile phase to

10% acetonitrile and 90% water, and later 8% acetonitrile and 92% water, was determined, whilst maintaining a flow rate of 1.5 mL/min.

2.12.6 Determination of rate constant

A stock solution of 200 mL was prepared from 0.4mL Lincocin® (lincomycin hydrochloride) and 20mL 1M HCl made up to volume with milliQ water and placed in a 60°C water bath. Samples were taken at time zero (control) and at selected time intervals over 12 days. Neutralised 5 mL aliquots taken from each sample were analysed by HPLC using the mobile phase, flow rate and wavelength outlined in Section 2.12.2. The semi-logarithmic plot of data obtained was used to determine the rate constant.

Relationships were generated using Origin® computer software and the graphical method was used to confirm the order of the reaction, which was *a priore* assumed to be a first order reaction. Rate constants were obtained from the slopes of the log concentration or log percent concentration against time plots. The Origin® computer software was used to obtain regression analysis of data using unweighted least squares**.**

A first order reaction can be represented as:

$$A \longrightarrow \text{products}$$

The rate of the reaction (dc/dt) is proportional to the concentration of A and the rate equation can be written as:

$$\frac{dc}{dt} = kc \qquad \text{(Equation 2.1)}$$

Where

k = the first order velocity constant

c = the concentration of starting material remaining undecomposed at time t

If Equation 2.1 is integrated between concentrations c_o and time t = 0 and concentration c and a later time t, this can be mathematically represented as:

$$\int_{c_o}^{c} \frac{dc}{c} = -k \int_{0}^{t} dt \qquad \text{(Equation 2.2)}$$

$$\ln c - \ln c_o = -k\,(t - 0) \qquad \text{(Equation 2.3)}$$

$$\ln c = \ln c_o - k\,t \qquad \text{(Equation 2.4)}$$

By converting Equation 2.4 to common logarithms, this yields Equation 2.5:

$$\log c = -\log c_o - kt / 2.303 \qquad \text{(Equation 2.5)}$$

Which can also be written as:

$$k = \frac{2.303}{t} \log \frac{c_o}{c} \qquad \text{(Equation 2.6)}$$

Written in an exponential form, Equation 2.5 becomes $c = c_o e^{-kt}$ so that for a first order reaction, the concentration of starting material decreases exponentially with time (Figure 2.1). If the logarithm of the concentration against time is plotted, a straight line is produced. The slope of the line is $-k/2.303$ and from this, the rate constant can be calculated.

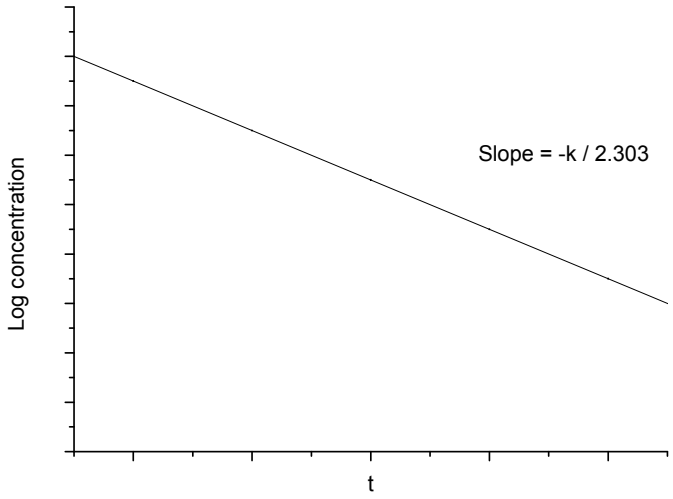


Figure 2-1 - First order reaction linear plot of log concentration versus time.[110]

The shelf-life, which is taken as the time for decomposition of the initial 10% of the active drug to occur, to leave 90% of the activity, is calculated using the formula when a first-order reactions occurs (Equation 2.7):

$$t_{90} = \frac{0.105}{k} \qquad \text{(Equation 2.7)}$$

A second order reaction of the form of Equation 2.8 can be rendered pseudo-first order by maintaining the concentration of B constant using buffers or where the concentration of B is in large excess of the concentration of A.

$$A + B \rightarrow \text{products} \qquad \text{(Equation 2.8)}$$

2.12.7 Stability in IV solutions

2.12.7.1 Accelerated stability testing in IV solutions

To test the stability of lincomycin hydrochloride in 0.9% NaCl and sodium lactate (Hartmann's) intravenous solutions, 0.4mL Lincocin® (lincomycin hydrochloride) was made to 200 mL with 0.9% sodium chloride or sodium lactate (Hartmann's) solution and placed in a 60°C water bath. Samples were taken at time zero (control) and several times daily for 8 days for HPLC and pH measurements. The mobile phase, flow rate and wavelength outlined in Section 2.12.2 were used to analyse 5 mL aliquots taken from each sample.

2.12.7.2 One-month stability testing at room temperature (25°C)

Stock solutions were prepared by measuring 0.4mL Lincocin® (lincomycin hydrochloride) and making up to 200mL with either sodium lactate (Hartmann's) solution, 0.9% sodium chloride solution, 5% glucose solution or 10% glucose solution. Each stock solution was placed in a 25°C water bath. Two 5 mL samples were taken at time zero (control), then every third day for 13 days and finally every fourth day thereafter until 31 days. One 5 mL sample was used neat to test pH and the other sample was made up to 10 mL with milliQ water and repeat analysed by HPLC using conditions outlined in Section 2.12.6. Each sample was analysed three times by HPLC.

2.12.8 Lincomycin hydrochloride stability in buffer solutions

2.12.8.1 Preparation of buffer solutions

Preparation of buffers used for this research was based on the Henderson-Hasselbach equation for a weak acid and its salt.[110]

$$pH = pK_a + \log \frac{[salt]}{[acid]} \qquad \text{(Equation 2.9)}$$

where pK_a, the negative logarithm of K_a, is the dissociation constant of the weak acid.

Buffers were prepared at pH 2.00, 3.10, 4.00, 6.10 and 8.00 to determine the effect of the buffer species on degradation of lincomycin hydrochloride. The analysis was carried out at each specified pH, 80°C and ionic strength of 0.5 mol/L sodium chloride. In this study, the buffer solutions used were:

- pH 2.00 buffer solution prepared from hydrochloric acid and sodium chloride.
- pH 3.10 buffer solution prepared from citric acid and sodium chloride.
- pH 4.00 acetate buffer solution prepared from acetic acid, sodium chloride and sodium hydroxide.
- pH 6.10 and 8.00 phosphate buffer solutions prepared from orthophosphoric acid, sodium chloride and sodium hydroxide.

The amount of sodium chloride required was calculated according to the following equation:

$$\mu = \tfrac{1}{2} \sum_{1}^{j} c_i z_i^2 \qquad \text{(Equation 2.10)}$$

Where:

μ is the ionic strength.

$\sum$ is the summation of the product of cz^2 terms for all the ionic species in the solution, from the first one to the *j*th species.

c_i is the concentration in moles/ litre of any of the ions.

z_i is the valence of the species.

2.12.9 pH measurements

Routine measurements of pH were carried out at room temperature for 5 mL samples and buffer solutions using a digital pH meter. Prior to pH measurements the instrument was standardised using standard buffer solutions. Each pH measurement was made prior to HPLC analysis and was taken at precisely 10 minutes using a stop watch.

Chapter 3
Evaluation of Off-label and Unlicensed prescribing at Princess Margaret Hospital

3.1 Patient demographics

1038 medical records were reviewed. One case, a 19-year old male, who was receiving ongoing care at PMH for cystic fibrosis, was excluded from the study due to age. Of the 1037 medical records, 607 (58.5%) were from males and 430 (41.5%) from females (Figure 3.1). The age of paediatric patients ranged from zero (newborn) up to and including 18 years. The distribution in yearly intervals is shown in Figure 3.2.

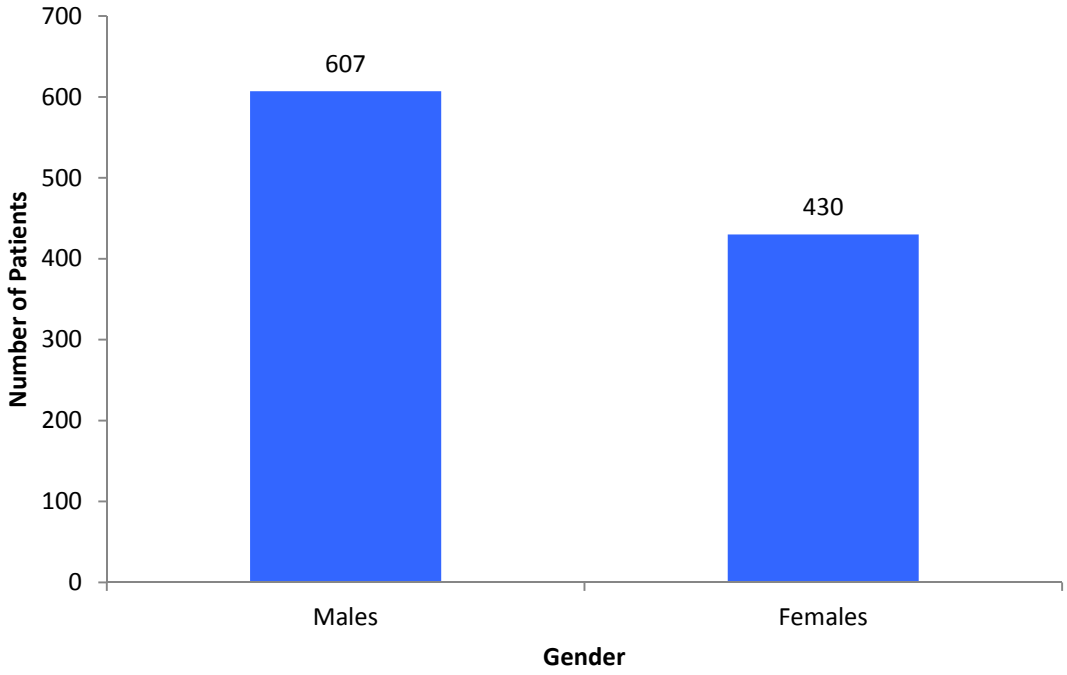


Figure 3-1 - Number of male and female patients.

Figure 3.2 shows that there were more patients in the zero to 0.99 years (152 patients) and 1 - 1.99 years (140 patients) age group than any other age group. The least number of patients were in the 18 - 18.99 years age group.

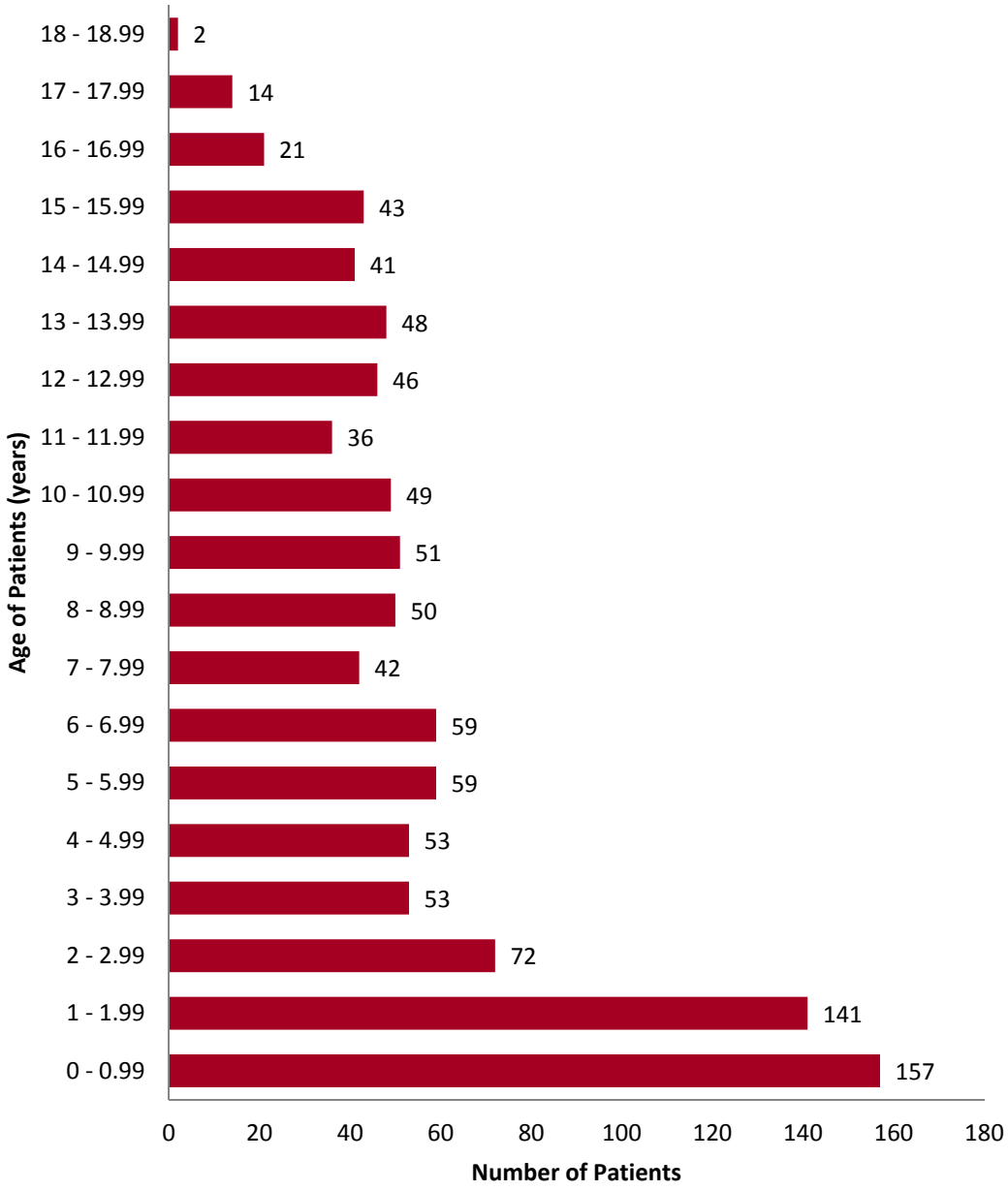


Figure 3-2 - Distribution of age.

For ease of analysis, age of patients was classified into four groups according to the European Medicines Agency (EMA).[6] Figure 3.3 shows that the majority of patients were aged between 2 and 11 years (524 patients).

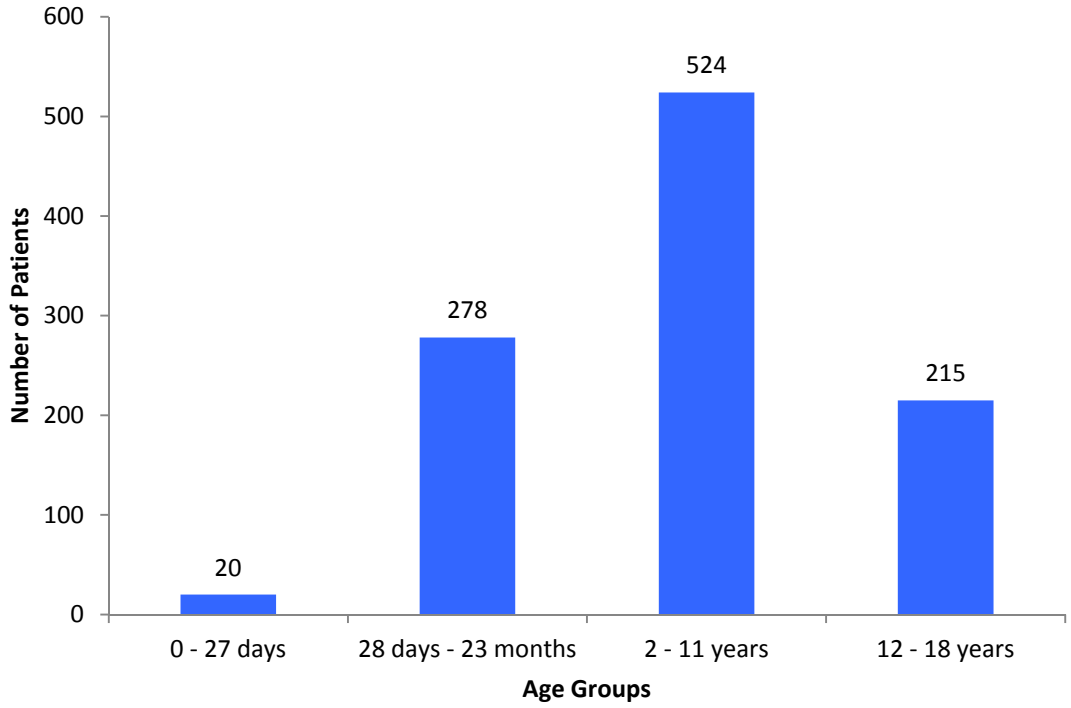


Figure 3-3 - Distribution of the four age groups using the EMA age classification system.[6]

The distribution of patients in each hospital setting (ie inpatient, outpatient and Emergency Department) is summarised in Table 3.1. Most records (n = 403; 38.9%) were from the Emergency Department; 36.6% from outpatients (n = 380) and 24.5% from inpatients (n = 254). Figure 3.4 shows that males made up a majority in each setting (57.8% in ED, 54.7% outpatients, 65.4% inpatients) and this was significant (p = 0.0272).

Table 3.1 - Distribution of male and female patients in the Emergency Department, inpatient and outpatient settings.

Gender	Emergency (n = 403) (%)		Inpatient (n = 254) (%)		Outpatient (n = 380) (%)		p
Male (n = 607; 59%)	233	57.8	166	65.4	208	54.7	0.0272
Female (n = 430; 41%)	170	42.2	88	34.6	172	45.3	

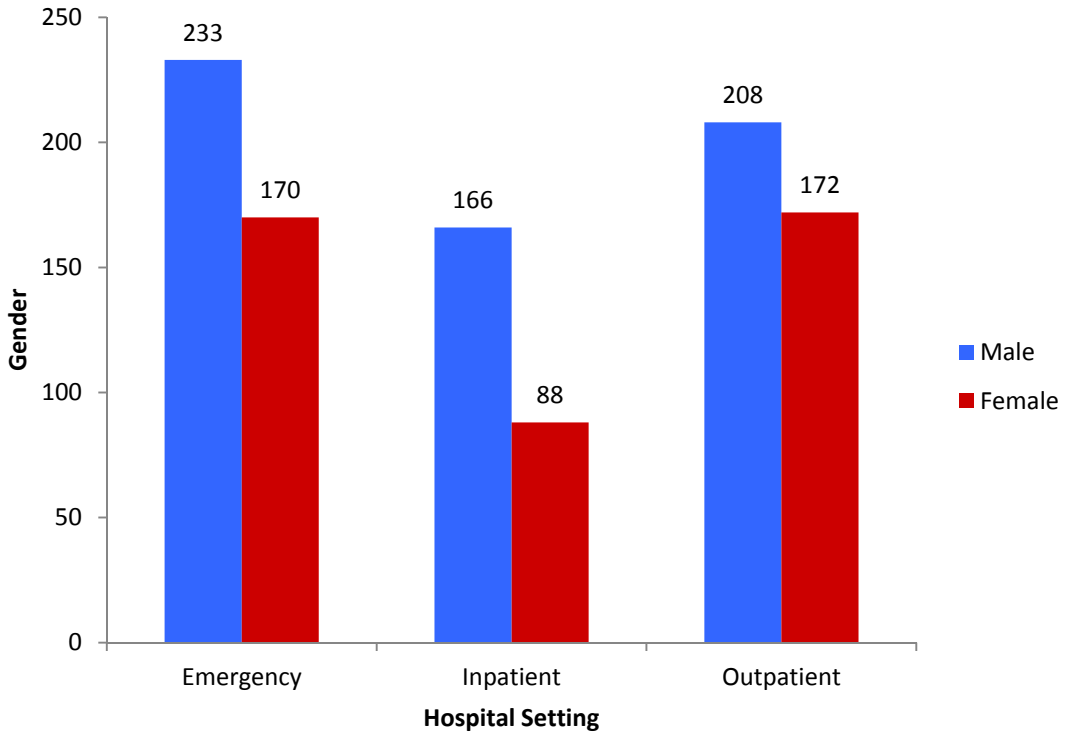


Figure 3-4 - Number of male and female patients in each hospital setting.

The single year age distribution of inpatients, outpatients or Emergency Department admissions is shown in Figure 3.5. In the Emergency Department, the highest numbers of admissions were for patients under three years of age with a majority aged between 1 and 1.99 years.

The largest number of inpatients was seen for patients aged less than one year (i.e. 0 – 0.99 years). There were no inpatients or Emergency Department admissions for anyone aged between 18 and 18.99 years. However, there were two outpatients aged between 18 and 18.99 year. The greatest numbers of outpatients were aged between one and two years (i.e. 1 – 1.99 years). There were also a greater number of outpatients aged less than one year (i.e. 0 – 0.99 years) and between nine and ten (i.e. 9 - 9.99) years of age.

For ease of analysis, the age of patients was grouped into four categories according to the EMA classification[6] and the distribution in each hospital setting recorded. Figure 3.6 shows the distribution of inpatients, outpatients and Emergency Department admissions for neonates (zero to 27 days), infants (28 days to 23 months), children (two to 11 years) and adolescents (12 to 18 years). When patients were grouped in this way, the majority of patients in each setting (i.e. inpatients, outpatients and Emergency Department patients) were aged between two to 11 years.

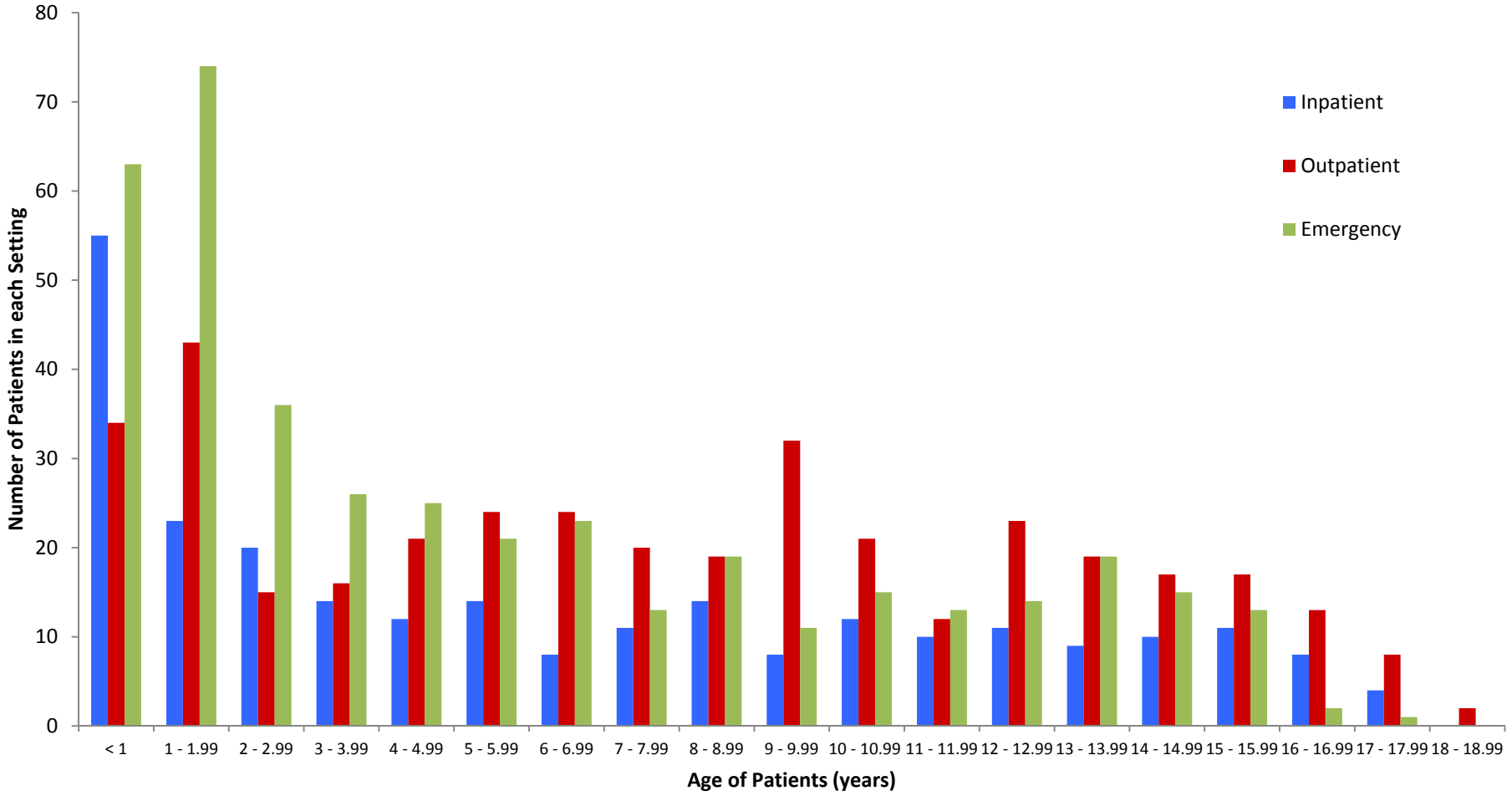


Figure 3-5 - Distribution of various age groups of patients seen in the Emergency Department, as inpatients and outpatients.

74

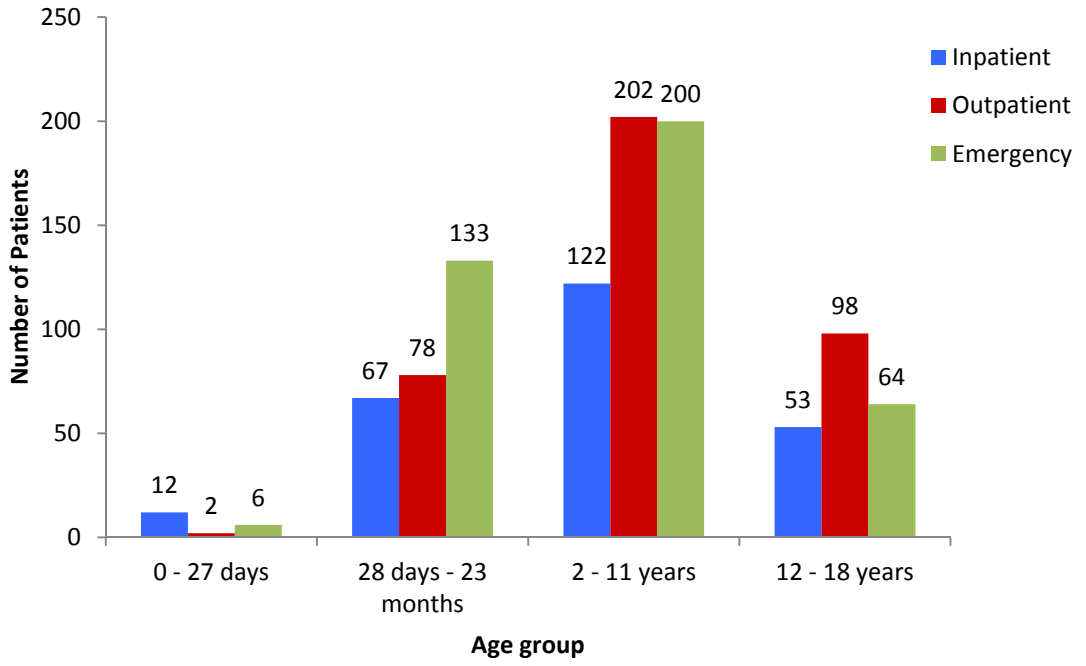


Figure 3-6 - Frequency of various age groups of patients seen in the Emergency Department, as inpatients and outpatients, according to the EMA classification.

The youngest patient, a newborn, was admitted as an inpatient and the oldest patient (18.4 years) was seen as an outpatient. The average age of all patients was 6.6 years (± 5.19 s; range 0.00 - 18.43). The average age of patients in the Emergency Department, inpatients and outpatients is shown in Table 3.2. The mean age was lowest for Emergency Department admissions (5.58 ± 4.83 years) and highest for outpatients (7.82 ± 5.16years). The median age was lowest for Emergency Department admissions (3.98 years) and highest for outpatients (7.77 years) (Table 3.3).

Table 3.2 - Mean age (± 1 standard deviation) of patients in Emergency Department admissions, inpatients and outpatients.

Mean age (years)					
Emergency		**Inpatient**		**Outpatient**	
(n = 403)	SD	(n = 254)	SD	(n = 380)	SD
5.58	± 4.83	6.39	± 5.44	7.82	± 5.16

The median age was lower than the mean age for Emergency Department patients and inpatients but it was slightly higher than outpatients (Table 3.3).

Table 3.3 - Median age of patients in Emergency Department admissions, inpatients and outpatients.

Median age (years)		
Emergency	**Inpatient**	**Outpatient**
(n = 403)	(n = 254)	(n = 380)
3.98 (Range: 0 - 17.07)	5.36 (Range:0 - 17.89)	7.77 (Range: 0.02 - 18.43)

A comparison of the mean ages between the three types of patients using Generalised Linear Model (GLM) analysis produced a significant result ($p < 0.001$) (Table 3.4) suggesting that patients seen in the Emergency Department were more likely to be younger than patients seen as inpatients or outpatients. Similarly, inpatients were more likely to be younger than outpatients ($p = 0.0003$).

Table 3.4 - Statistical analysis reported as probability data on age of Emergency Department admissions, inpatients and outpatients using GLM analysis, with age as a dependent variable.

	Emergency	**Inpatient**	**Outpatient**
Emergency		0.0491	< 0.0001
Inpatient	0.0491		0.0003
Outpatient	< 0.0001	0.0003	

3.2 Analysis of prescription drugs

A total of 2654 drugs were prescribed to 699 out of 1037 patients (67.4%). The 2654 drugs consisted of 330 different drugs (Appendix 4), which included licensed, off-label and unlicensed drugs.

All drugs were classified into the Anatomical Therapeutic Chemical (ATC) classification. Table 3.5 shows the frequency of drugs in each ATC category. The largest number of the 2654 drugs were classified into the nervous system (n = 1034; 39.0%), followed by the alimentary tract (n = 408; 15.4%), anti-infective (n = 400; 15.1%) and respiratory system (n = 180; 6.8%).

Table 3.5 - Frequency of all drugs, including licensed, off-label and unlicensed drugs, in each ATC category

ATC Code	Frequency (n = 2654)	%
Alimentary tract and metabolism	408	15.4
Blood and blood forming organs	34	1.3
Cardiovascular system	69	2.6
Dermatologicals	111	4.2
Genito-urinary system and sex hormones	19	0.7
Systemic hormonal preparations excl sex hormones	154	5.8
Anti-infectives for systemic use	400	15.1
Antineoplastics and immunomodulating agents	42	1.6
Musculo-skeletal system	73	2.8
Nervous system	1034	39.0
Antiparasitic products, insecticides and repellent	5	0.2
Respiratory system	180	6.8
Sensory organs	95	3.6
Various	30	1.1

The age distribution for all drugs prescribed is shown in Figure 3.7. The greatest percentage of drugs were prescribed to children (aged 2 to 11 years), followed by adolescents (aged 12 to 18 years). The least number of drugs were prescribed to neonates (aged zero to 27 days).

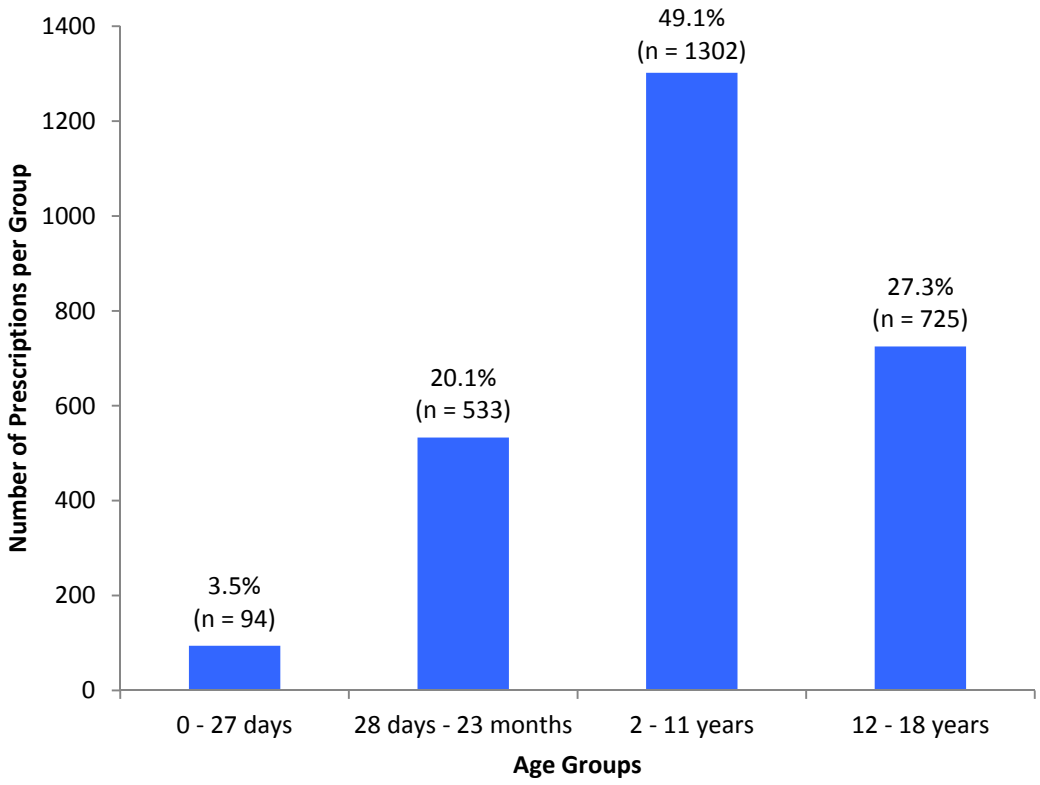


Figure 3-7 - Number of drugs prescribed to various age groups of paediatric patients.

Of the 2654 drugs, the majority (n = 1905, 71.8%) were licensed, 681 (25.7%) were off-label and 68 (2.6%) unlicensed (Figure 3.8).

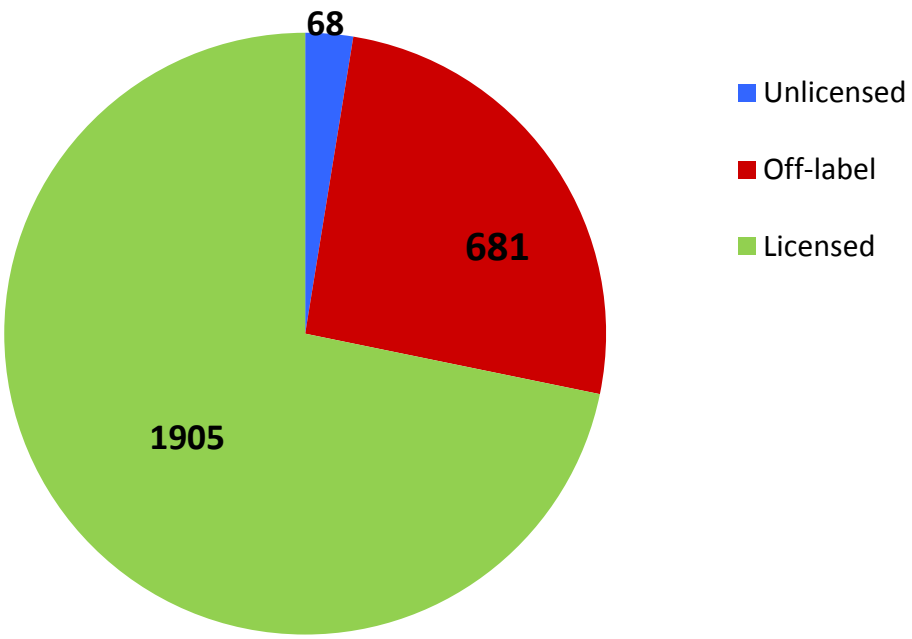


Figure 3-8 - Number of drugs that were prescribed licensed, off-label and unlicensed.

There were 121 different off-label drugs prescribed (Table 3.6).The most commonly prescribed off-label drug was ondansetron, followed by Painstop Day® (paracetamol 120 mg, codeine phosphate 5 mg per 5 mL) and salbutamol.

Table 3.6 - List of 121 off-label prescribed drugs.

Off-label Drug	Frequency	Off-label Drug	Frequency	Off-label Drug	Frequency
Aciclovir	5	Hydralazine	2	Ondansetron	94
Adrenaline	1	Hydrocortisone	1	Oxybutynin	1
Alfentanil	2	Hydroxyurea	1	Oxycodone	49
Alteplase	2	Hyoscine butylbromide	1	Painstop Day®	71
Amitriptyline	1	Ibuprofen	4	Painstop Night®	5
Amlodipine	1	Infliximab	1	Panadeine Forte®	1
Amoxicillin	18	Interferon beta	1	Pantoprazole	2
Aprepitant	3	Ipratropium	12	Paracetamol	48
Atorvastatin	1	Ketamine	1	Parachoc®	1
Augmentin duo®	3	Lactulose	3	Parecoxib	2
Azithromycin	1	Lamotrigine	1	Pizotifen	1
Benzylpenicillin	2	Lansoprazole	2	Potassium chloride	1
Betamethasone	2	Latanoprost	1	Praziquantil	1
Betaxolol	1	Leuprorelin	1	Pregabalin	1
Brimonidine	1	Levetiracetam	2	Promethazine	3
Brinzolamide	1	Lignocaine	1	Propofol	7
Budesonide/ eformoterol	1	Lisinopril	1	Quetiapine	4
Calcium carbonate	1	Loratadine	3	Ranitidine	3
Captopril	1	Lorazepam	7	Risperidone	1
Carbimazole	1	Loperamide	1	Salbutamol	51
Cephalexin	2	Losartan	1	Sertraline	2
Chloral hydrate	3	Melatonin	1	Sildenafil	2
Chloramphenicol	4	Meropenem	1	Solifenacin	2
Clonidine	13	Methotrexate	2	SOOV IT®	1
Ciprofloxacin	1	Metoclopramide	12	Teicoplanin	1
Clobazam	3	Metronidazole	3	Temazepam	5
Codeine	10	Microlax®	2	Terbinafine	1
Darbapoetin	1	Midazolam	29	ticarcillin/ potassium clavulanate	19
Dexamethasone	6	Minoxidil	1	Timolol	1
Dopamine	3	Mirtazapine	1	Tolterodine	1
Epipen® junior	1	Montelukast	1	Tropisetron	1
Escitalopram	1	Morphine	3	Tobramycin	7
Fentanyl	21	Mupirocin	2	Topotecan	2
Flucloxacillin	18	Natalizumab	1	Tropicamide	1
Fluorometholone	1	Nifedipine	2	Valaciclovir	1
Fluorouracil	1	Nitrazepam	1	Valganciclovir	1
Fluoxetine	4	Octreotide	1	Vancomycin	5
Gabapentin	2	Ofloxacin	1	Vigabatrin	1
Gentamicin	8	Olanzapine	2	Vitabdeck®	2
Glyceryl trinitrate	1	Omeprazole	10	Xalacom®	1

All off-label drugs were classified into the appropriate ATC category (Table 3.7). The majority of off-label drugs (n = 295; 43.3%) were classified into the nervous system. This classification included analgesic drugs such as Painstop®, oxycodone and paracetamol, which were the most commonly off-label prescribed nervous system drugs. The next most frequent off-label ATC classifications were the alimentary tract (n = 139; 20.4%) and anti-infectives (97 i.e. 14.2%).

Table 3.7 - Frequency of off-label drugs in each ATC category.

ATC Code of off-label drugs	Frequency (n = 681)	%
Alimentary tract and metabolism	139	20.4
Blood and blood forming organs	3	0.4
Cardiovascular system	28	4.1
Dermatologicals	7	1.0
Genito-urinary system and sex hormones	7	1.0
Systemic hormonal preparations excl sex hormones	3	0.4
Anti-infectives for systemic use	97	14.2
Antineoplastics and immunomodulating agents	9	1.3
Musculo-skeletal system	2	0.3
Nervous system	295	43.3
Antiparasitic products, insecticides and repellent	1	0.2
Respiratory system	71	10.4
Sensory organs	19	2.8
Various	0	0

The 68 drugs prescribed in an unlicensed manner included 22 different drugs (Table 3.8). The most commonly prescribed unlicensed drugs were dexamethasone and dilacaine (29.4% and 17.7% respectively).

Table 3.8 - List of 22 different unlicensed drugs

Unlicensed Drug	Frequency (n = 68)	%
Adrenaline	7	10.3
Aspirin	2	2.9
Azathioprine	2	2.9
Carnitine	3	4.4
Cephazolin	1	1.5
Cisretinoic acid	1	1.5
Dexamethasone	20	29.4
Dilacaine	12	17.7
Domperidone	2	2.9
Gonadorelin	2	2.9
Magnesium chloride	1	1.5
Metolazone	1	1.5
Picibanil (OK 432)	1	1.5
Potassium chloride	2	2.9
Propranolol	1	1.5
Salicyclic acid/ cetylpyridium chloride	1	1.5
Sodium bicarbonate	1	1.5
Sodium chloride	4	5.9
Tacrolimus	1	1.5
Tinidazole	1	1.5
Tocilizumab	1	1.5
Trichloracetic acid paste APF	1	1.5

All unlicensed drugs were classified into the appropriate ATC category (Table 3.9). The majority of unlicensed drugs were systemic hormonal preparations excluding sex hormones (n = 22, 32.4%) and sensory organ drugs (n = 13, 19.1%). Alimentary tract and metabolism drugs were also prescribed frequently in an unlicensed manner (n = 11; 16.2%)

Since the prevalence of off-label prescribing was 25.7% and the prevalence of unlicensed prescribing 2.6%, therefore the overall extent of off-label and unlicensed prescribing across the three settings was 28.3%.

Table 3.9 - Frequency of unlicensed drugs in each ATC category

ATC Code of unlicensed drugs	Frequency (n = 68)	%
Alimentary tract and metabolism	11	16.2
Blood and blood forming organs	3	4.4
Cardiovascular system	4	5.9
Dermatologicals	3	4.4
Genito-urinary system and sex hormones	2	2.9
Systemic hormonal preparations excl sex hormones	22	32.4
Anti-infectives for systemic use	1	1.5
Antineoplastics and immunomodulating agents	5	7.4
Musculo-skeletal system	0	0.0
Nervous system	0	0.0
Antiparasitic products, insecticides and repellent	0	0.0
Respiratory system	3	4.4
Sensory organs	13	19.1
Various	1	1.5

3.3 Prescribing trends - considering the patients

Of the 1037 patients involved in the study, the number of patients in each setting (inpatients, outpatients, Emergency Department patients) that did not receive any drugs or that received some drugs, including licensed, off-label and unlicensed drugs, is shown in Figure 3.9. Three hundred and thirty eight patients did not receive any drugs and of these 12 were inpatients, 173 were outpatients and 153 were Emergency Department patients. In each setting more patients received some drugs as opposed to no drugs. When only inpatients were considered, 95.3% received some drugs whereas 62.0% of Emergency Department patients received some drugs rather than no drugs. However, when only outpatients were considered, there was no statistical difference difference between outpatients that received no drugs or some drugs 45.5% and 54.5% respectively). Overall, the data were significant ($p < 0.0001$).

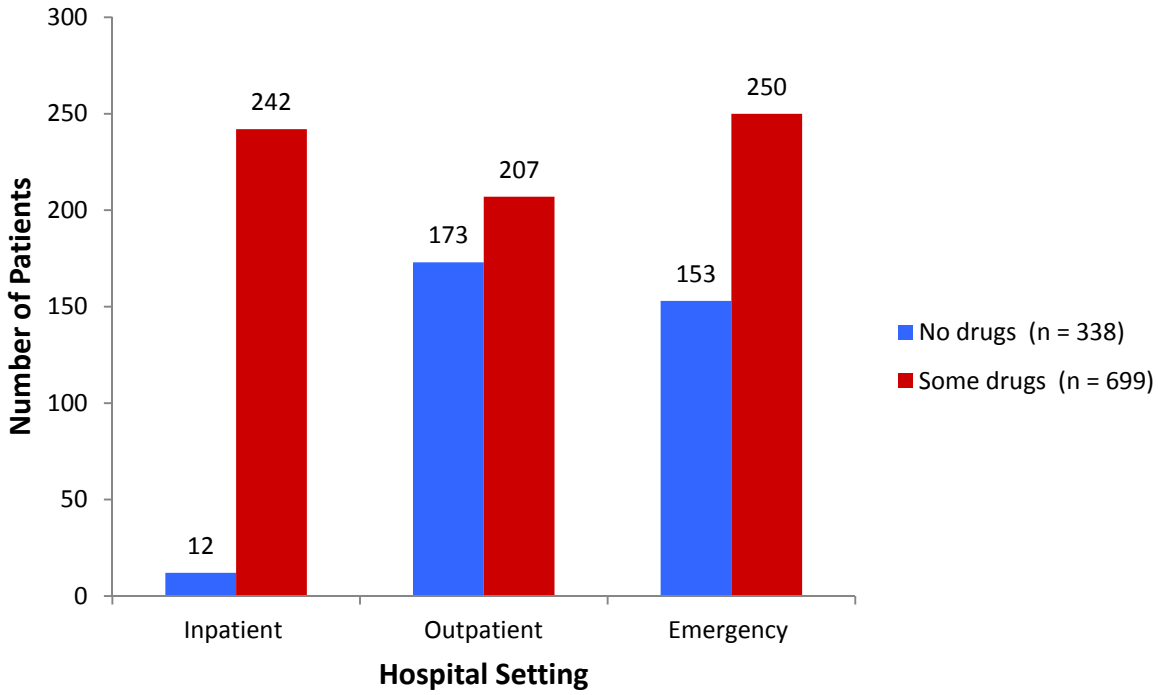


Figure 3-9 - Number of patients in each hospital setting receiving no drugs or some drugs (at least one or more drugs)

The number of male and female patients that received no drugs or some drugs (including licensed, off-label and unlicensed drugs) is shown in Figure 3.10. Of the 1037 patients, 189 males (31.1%) and 149 females (34.7%) did not receive any drugs. Of the 699 patients that received some drugs, 418 were males (59.8%) and 281 were females (40.2%).

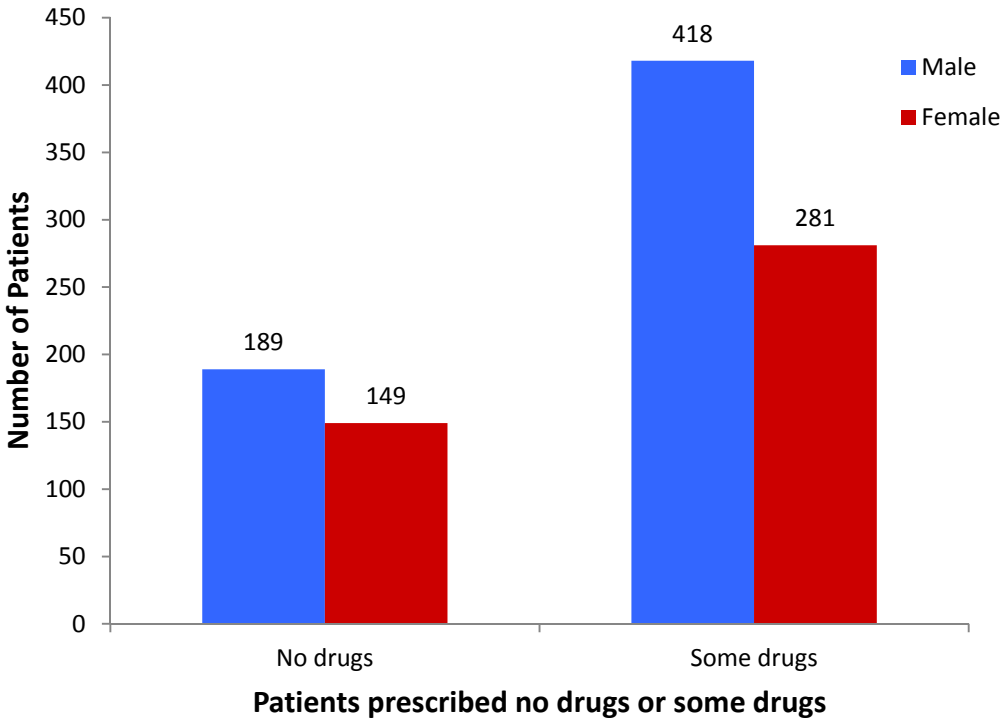


Figure 3-10 -Gender distribution of patients that received no drugs or some drugs.

When the drugs administered to patients were grouped into licensed and off-label/ unlicensed drugs to determine if there was a difference in the number of male and female patients that received no drugs, licensed drugs or off-label/ unlicensed drugs, the percentage of males that were prescribed no drugs or licensed drugs (31.1% and 30.0% respectively) was marginally less than females (34.7% and 32.3% respectively) but the finding was not significant (p = 0.1520) (Table 3.10). The percentage of off-label/ unlicensed drugs was also similar for gender (38.9% males, 33.0% females).

Table 3.10 - Gender distribution of the number of patients receiving no drugs, licensed drugs or off-label/ unlicensed drugs.

Gender	No Drugs (n = 338)		Licensed Drugs (n = 321)		Off-label/ unlicensed Drugs (n = 378)	
Male (n = 607)(%)	189	31.1	182	30.0	236	38.9
Female (n = 430)(%)	149	34.7	139	32.3	142	33.0

p = 0.1520

Table 3.10 was modified to separate the number of patients receiving off-label/ unlicensed drugs to determine the number in each classification (Table 3.11). This showed that more females were prescribed unlicensed drugs (4.7% compared to 2.5%) but a greater percentage of males were prescribed off-label drugs (36.4% compared to 28.4%). The results were significant (p = 0.0198).

Table 3.11 - Gender distribution of the number of patients prescribed no drugs, licensed drugs and off-label or unlicensed drugs.

Gender	No Drugs (n = 338)		Licensed Drugs (n = 321)		Off-label Drugs (n = 343)		Unlicensed Drugs (n = 35)	
Male (n = 607) (%)	189	31.1	182	30.0	221	36.4	15	2.5
Female (n = 430) (%)	149	34.7	139	32.3	122	28.4	20	4.7

p = 0.0198

Figure 3.11 shows the age distribution of patients that were prescribed no drugs, licensed, off-label and unlicensed drugs. Of the 20 patients aged zero to 27 days, 12 patients (60.0%) were prescribed off-label drugs. This may not be representative of all patients in this age group in general as the sample size was too small. The highest percentage of off-label prescribing occurred in infants (28 days to 23 months) and children (two to 11 years) (31.7% and 35.9% respectively) and the highest percentage of unlicensed prescribing (7.2%) occurred in infants (28 days to 23 months). The results were significant ($p < 0.0001$).

Table 3.12 shows the number of inpatients, outpatients and Emergency Department patients that received no drugs, licensed, off-label or unlicensed drugs. The highest percentage of off-label drugs were prescribed to inpatients (74.4%). The percentage of unlicensed drugs prescribed was the similar (3.1%, 3.4% and 3.5%) in each of the three settings. The differences in prescribing in the three settings were significant ($p < 0.0001$).

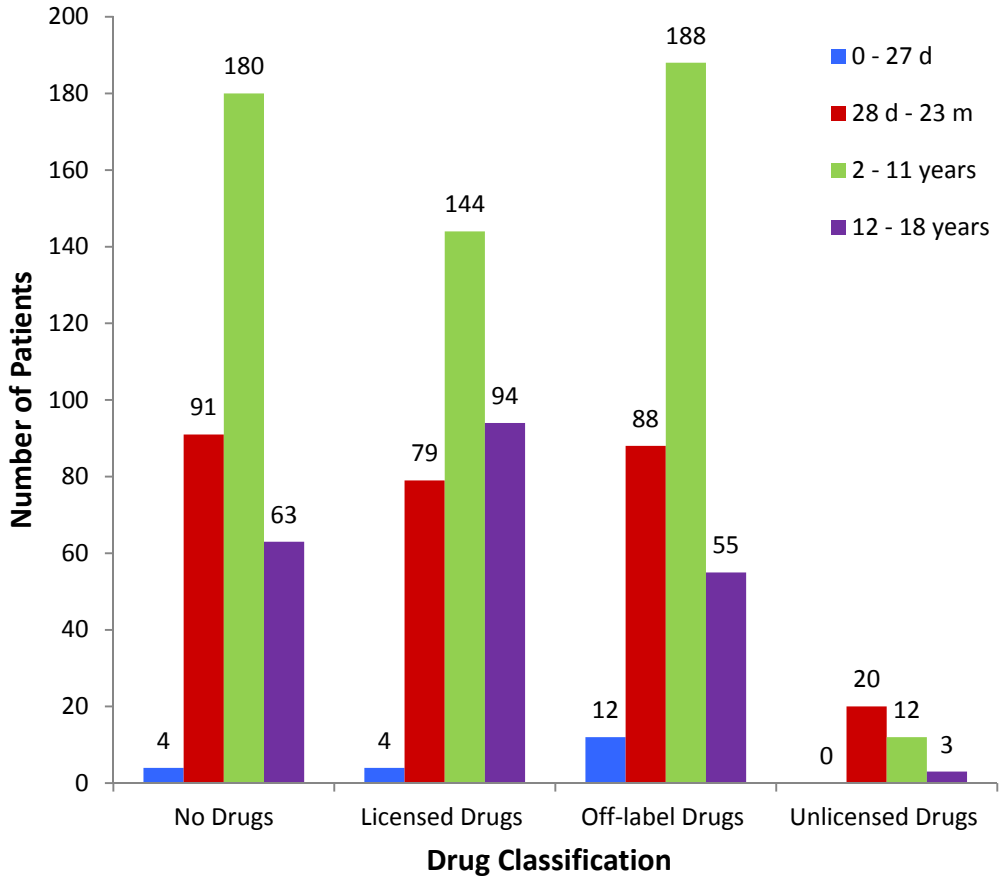


Figure 3-11 -Number of patients in various age groups prescribed no drugs, licensed, off-label or unlicensed drugs.

Table 3.12 - Number (%) of patients in each setting receiving no drugs, licensed, off-label or unlicensed drugs.

Setting (n = 1037)	**No Drugs** (n = 338)		**Licensed Drugs** (n = 321)		**Off-label Drugs** (n = 343)		**Unlicensed Drugs** (n = 35)	
Inpatient (n = 254) (%)	12	4.7	45	17.7	189	74.4	8	3.1
Outpatient (n = 380) (%)	173	45.5	139	36.6	55	14.5	13	3.4
Emergency (n = 403) (%)	153	37.9	137	34.0	99	24.6	14	3.5

$p < 0.0001$

The data were further classified to determine gender differences in each setting (inpatients, outpatients and emergency) (Table 3.13). Of the 403 Emergency Department admissions, 250 patients received drugs and of these, 113 (45.2%) received some off-label/ unlicensed drugs. In considering only the 143 male and 107 female Emergency Department patients that received drugs, 68 (47.6%) males and 45 (42.1%) females received one or more off-label or unlicensed drugs.

Table 3.13 - Gender distribution in each setting that were prescribed no drugs, licensed and off-label/ unlicensed drugs.

Setting	Gender	No Drugs		Licensed Drugs		Off-label/ unlicensed Drugs	
	(n = 1037)	(n = 338)		(n = 321)		(n = 378)	
Inpatient (n = 254)	**Male** (n = 166) (%)	8	4.8	29	17.5	129	77.7
	Female (n = 88) (%)	4	4.5	16	18.2	68	77.3
Outpatient (n = 380)	**Male** (n = 208) (%)	91	43.8	78	37.5	39	18.8
	Female (n = 172) (%)	82	47.7	61	35.5	29	16.9
Emergency (n = 403)	**Male** (n = 233) (%)	90	38.6	75	32.2	68	29.2
	Female (n = 170) (%)	63	37.0	62	36.5	45	26.5

Of the 380 outpatients, 207 patients received some drugs and of these, 68 (32.8%) received some off-label or unlicensed drugs. In considering only the 117 male and 90 female outpatients that received some drugs, 33.3% of males and 32.2% of females received one or more off-label or unlicensed drugs.

Table 3.13 shows that the percentages of off-label or unlicensed prescribing between male and female inpatients were similar (77.7% for males and 77.3% for females). However, in considering only the 242 (95.3%) inpatients that were prescribed drugs, 197 (81.4%) received some off-label or unlicensed drugs. In considering only the 158 male and 84 female inpatients that received some drugs, 81.6% of males and 81.0% of females received one or more off-label or unlicensed drugs.

To determine if there were gender differences in each setting as well as differences in the types of drugs prescribed, the drugs shown in Table 3.13 as off-label/ unlicensed drugs were separated (Table 3.14).

Table 3.14 shows that a greater percentage of female inpatients and outpatients were prescribed unlicensed drugs (5.7% and 5.8% respectively compared to 1.8% inpatient males and 1.4% outpatient males) but a greater percentage of Emergency Department males were prescribed unlicensed drugs (3.9% compared to 2.9% females). However, a greater percentage of inpatient and outpatient males were prescribed off-label drugs (75.9% and 17.3% respectively compared to 71.6% female inpatients and 11.0% female outpatients). The percentage of Emergency Department male and female patients prescribed off-label drugs were the same. Differences for male and female outpatients were significant ($p = 0.0414$) but not for inpatients ($p = 0.4056$) or Emergency Department patients ($p = 0.8103$).

Table 3.14 - Number of males and females in each setting that were prescribed no drugs, licensed, off-label or unlicensed drugs

Setting	Gender	No drug (n = 338)		Licensed Drugs (n = 321)		Off-label Drugs (n = 343)		Un-licensed Drugs (n = 35)		p
Inpatient (n = 254)	**Male** (n = 166) (%)	8	4.8	29	17.5	126	75.9	3	1.8	0.4056
	Female (n = 88) (%)	4	4.5	16	18.2	63	71.6	5	5.7	
Outpatient (n = 380)	**Male** (n = 208) (%)	91	43.8	78	37.5	36	17.3	3	1.4	0.0414
	Female (n = 172) (%)	82	47.7	61	35.5	19	11.0	10	5.8	
Emergency (n = 403)	**Male** (n = 233) (%)	90	38.6	75	32.2	59	25.3	9	3.9	0.8103
	Female (n = 170) (%)	63	37.1	62	36.5	40	23.5	5	2.9	

The age groups of patients in each setting (inpatients, outpatients and Emergency Department patients) and the type of drug prescribed is summarised in Table 3.15. For inpatients, each of the four age groups were prescribed more off-label drugs than licensed drugs. The inpatient age groups with the highest percentage of off-label prescribing were children aged two to 11 years (85.2%) and neonates aged zero to 27 days (83.3%). Only eight of the 254 inpatients (3.1%) were prescribed unlicensed drugs (but not any off-label drugs). The age group with the highest percentage of unlicensed prescriptions were infants aged 28 days to 23 months (7.5%). The differences in the type of drugs prescribed to inpatients in various age groups was significant (p = 0.0077).

Table 3.15 - Category of drugs prescribed to various age groups of inpatients, outpatients and Emergency Department patients.

Setting	Age group	No drug (n = 338)		Licensed Drugs (n = 321)		Off-label Drugs (n = 343)		Un-licensed Drugs (n = 35)		p
Inpatient	**0 - 27 d** (n = 12) (%)	1	8.3	1	8.3	10	83.3	0	0	0.0077
	28d - 23 m (n = 67) (%)	3	4.5	16	23.9	43	64.2	5	7.5	
	2 - 11 y (n = 122) (%)	5	4.1	12	9.8	104	85.2	1	0.8	
	12 - 18 y (n = 53) (%)	3	5.7	16	30.2	32	60.4	2	3.8	
Outpatient	**0 - 27 d** (n = 2) (%)	0	0	1	50.0	1	50.0	0	0	0.0004
	28d - 23 m (n = 78) (%)	35	44.9	21	26.9	13	16.7	9	11.5	
	2 - 11 y (n = 202) (%)	101	50.0	70	34.7	28	13.9	3	1.5	
	12 - 18 y (n = 98) (%)	37	37.8	47	48.0	13	13.3	1	1.0	
Emergency	**0 - 27 d** (n = 6) (%)	3	50.0	2	33.3	1	16.7	0	0	0.2514
	28d - 23 m (n = 133) (%)	53	39.8	42	31.6	32	24.1	6	4.5	
	2 - 11 y (n = 200) (%)	74	37.0	62	31.0	56	28.0	8	4.0	
	12 - 18 y (n = 64) (%)	23	35.9	31	48.4	10	15.6	0	0	

Significant differences were also found for outpatients. More outpatients aged 28 days to 23 months and two to 11 years were not prescribed any drugs at all (44.9% and 50.0% respectively). There were only two outpatient neonates in the study aged zero to 27 days, one of which was prescribed a licensed drug and the other an off-label drug. No neonate was prescribed an unlicensed drug. More outpatients aged 28 days to 23 months were prescribed unlicensed drugs (11.5%). The differences in the type of drugs prescribed to outpatients in various age groups was significant ($p = 0.0004$).

The percentage of Emergency Department patients in the various age groups prescribed off-label drugs was similar and ranged from 15.6% (patients aged 12 to 18 years) to 28.0% (patients aged two to 11 years). No unlicensed drugs were prescribed to neonates aged zero to 27 days and adolescents aged 12 to 18 years. However, 4.5% of unlicensed drugs were prescribed to infants aged 28 days to 23 months and 4.0% to children aged two to 11 years. No significant differences were found in prescribing trends for Emergency Department patients in the various age groups ($p = 0.2514$).

Table 3.16 shows that the inpatient gender and age groups with the highest percentage of off-label or unlicensed prescribing were males aged zero to 27 days (66.7%) and males aged two to 11 years (58.2%).

Table 3.16 - Number of patients in different age groups and in different settings prescribed no drugs, licensed, off-label or unlicensed drugs.

Setting	Age group	Gender	No drugs (n = 338)		Licensed Drugs (n = 321)		Off-label or unlicensed drugs (n = 378)	
Inpatient	**0 - 27 d**	Male	0	0.0	1	8.3	8	66.7
	(n = 12) (%)	Female	1	8.3	0	0.0	2	16.7
	28d - 23 m	Male	3	4.5	8	11.9	28	41.8
	(n = 67) (%)	Female	0	0	8	11.9	20	29.9
	2 - 11 y	Male	2	1.6	10	8.2	71	58.2
	(n = 122) (%)	Female	3	2.5	2	1.6	34	27.9
	12 - 18 y	Male	3	5.7	10	18.9	22	41.5
	(n = 53) (%)	Female	0	0.0	6	11.3	12	22.6
Outpatient	**0 - 27 d**	Male	0	0.0	1	50.0	1	50.0
	(n = 2) (%)	Female	0	0.0	0	0.0	0	0.0
	28d - 23 m	Male	20	25.6	13	16.7	12	15.4
	(n = 78) (%)	Female	15	19.2	8	10.3	10	12.8
	2 - 11 y	Male	50	24.8	38	18.8	17	8.4
	(n = 202) (%)	Female	51	25.2	32	15.8	14	6.9
	12 - 18 y	Male	21	21.4	26	26.5	9	9.2
	(n = 98) (%)	Female	16	16.3	21	21.4	5	5.1
Emergency	**0 - 27 d**	Male	2	33.3	1	16.7	0	0.0
	(n = 6) (%)	Female	1	16.7	1	16.7	1	16.7
	28d - 23 m	Male	29	21.8	23	17.3	22	16.5
	(n = 133) (%)	Female	24	18.0	19	14.3	16	12.0
	2 - 11 y	Male	41	20.5	31	15.5	37	18.5
	(n = 200) (%)	Female	33	16.5	31	15.5	27	13.5
	12 - 18 y	Male	18	28.1	20	31.2	9	14.1
	(n = 64) (%)	Female	5	7.8	11	17.2	1	1.6

3.4 Further analysis of patients classified as taking "off-label drugs"

According to the hierarchical classification system defined in Chapter 2 that was used to categorise patients into off-label or unlicensed drug categories, any patient administered an off-label drug in addition to an unlicensed drug was categorised into the off-label group so that each of the 1037 patients was categorised only into one single category (Chapter 2 Section 2.4.1). The data in Table 3.11 were analysed further to determine the number of patients categorised as receiving only off-label drugs and those that received both off-label and unlicensed drugs (Table 3.17). A comparison of male and female patients showed that a greater percentage of males were prescribed off-label only drugs (33.3% compared to 27.2% of females) as well as a combination of off-label and unlicensed drugs (3.1% compared to 1.2% of females) whereas a greater percentage of females were prescribed unlicensed drugs. The findings were significant (p = 0.0162).

Table 3.17 - Gender distribution of the number of patients prescribed no drugs, licensed, off-label, unlicensed or off-label and unlicensed drugs.

Gender	No Drugs (n = 338)		Licensed Drugs (n = 321)		Off-label Drugs (n = 319)		Unlicensed Drugs (n = 35)		Off-label & unlicensed Drugs (n = 24)	
Male (n = 607) (%)	189	31.1	182	30.0	202	33.3	15	2.5	19	3.1
Female (n = 430) (%)	149	34.7	139	32.3	117	27.2	20	4.7	5	1.2

p = 0.0162

Figure 3.15 shows that no patients aged zero to 27 days received only unlicensed drugs (according to the hierarchical classification system defined in the methodology in Chapter 2). To determine if there were any patients that were classified as 'off-label 'in this age group that received both off-label and unlicensed drugs, patients categorised into the off-label category were separated into those that received only off-label drugs and those that received both off-label and unlicensed drugs (Table 3.18).

Table 3.18 - Different age groups prescribed no drugs, licensed, off-label, unlicensed or off-label and unlicensed drugs.

Age group	No Drugs (n = 338)		Licensed Drugs (n = 321)		Off-label Drugs (n = 319)		Unlicensed Drugs (n = 35)		Off-label & unlicensed Drugs (n = 24)	
0 - 27 d (n = 20) (%)	4	20.0	4	20.0	11	55.0	0	0	1	5.0
28 d - 23 m (n = 278) (%)	91	32.7	79	28.4	77	27.7	20	7.2	11	4.0
2 - 11 years (n = 524) (%)	180	34.4	144	27.5	178	34.0	12	2.3	10	1.9
12 - 18 years (n = 215) (%)	63	29.3	94	43.7	53	24.7	3	1.4	2	1.0

$p < 0.0001$

Table 3.18 shows that one patient aged zero to 27 days was prescribed both unlicensed and off-label drugs. The infant was a two week old male inpatient prescribed cephazolin eye drops (unlicensed) and amoxicillin with clavulanic acid (off-label for age). Although an injection of cephazolin is available, for which the PI states that the safety for use in premature infants and infants under one month of age has not been established, no commercial formulation of cephazolin eye drops was available so these were compounded at the hospital. The PI for amoxicillin with clavulanic acid does not provide a dose for children under two months of age so the antibiotic was off-label for age.

When the patients classified as receiving off-label drugs in Table 3.12 were separated to show how many patients received only off-label drugs and how many received a combination of both off-label and unlicensed drugs (Table 3.19), a higher percentage of inpatients received a combination of off-label and unlicensed drugs (5.9%). The differences in the types of drugs prescribed with respect to setting was significant ($p < 0.0001$).

Table 3.19 - Number of patients in each setting receiving no drugs, licensed, off-label drugs only, unlicensed drugs only or off-label and unlicensed drugs.

Setting	No Drugs (n = 338; 32.6%)		Licensed Drugs (n = 321; 31.0%)		Off-label Drugs (n = 319; 30.8%)		Unlicensed Drugs (n = 35; 3.4%)		Off-label & unlicensed Drugs (n = 24; 2.3%)	
Inpatient (n = 254) (%)	12	4.7	45	17.7	174	68.5	8	3.1	15	5.9
Outpatient (n = 380) (%)	173	45.5	139	36.6	50	13.2	13	3.4	5	1.3
Emergency (n = 403) (%)	153	38.0	137	34.0	95	23.6	14	3.5	4	1.0

$p < 0.0001$

3.5 Prescribing trends - drugs prescribed

The number of drugs prescribed per person, including licensed drugs as well as off-label and unlicensed drugs, ranged from zero to twenty-one (Table 3.20). Almost one-third of patients were prescribed no drug (32.6%) and one to two drugs (20.7% and 12.8% respectively) were most frequent. The maximum number of drugs prescribed per person (21 drugs) were prescribed to seven different patients.

Table 3.20 - Number of patients that were prescribed different amounts of licensed, unlicensed and off-label drugs

Number of drugs	Number of patients (n = 1037)	%
0	338	32.6
1	215	20.7
2	133	12.8
3	88	8.5
4	69	6.7
5	33	3.2
6	49	4.7
7	21	2.0
8	21	2.0
9	16	1.5
10	12	1.2
11	12	1.2
12	10	1.0
13	3	0.3
14	2	0.2
15	2	0.2
16	5	0.5
19	1	0.1
21	7	0.7

Table 3.21 shows the number of drugs prescribed per inpatient, outpatient and Emergency Department patients. The majority of outpatients and Emergency Department patients were prescribed no drugs or one to two drugs. The maximum number of drugs prescribed to outpatients was twelve and to Emergency Department patients was sixteen. The results were very different for inpatients. The number of drugs prescribed for the 254 inpatients ranged from zero to 21 but few inpatients were prescribed no drug (4.7%). Frequently inpatients were prescribed three (11.0%), four (13.4%) or six (11.8%) drugs. Twenty one drugs were prescribed to seven inpatients. The differences in the number of drugs prescribed with respect to setting were significant ($p < 0.0001$).

Table 3.22 shows differences in the number of off-label drugs prescribed per person in each setting (inpatients, outpatients, Emergency Department). These findings were significant ($p < 0.0001$). Of the 699 patients that were prescribed drugs, 343 were prescribed off-label drugs and 356 were not prescribed any off-label drugs (53 inpatients, 152 outpatients and 151 emergency patients). A greater percentage of outpatients and Emergency Department patients were not prescribed any off-label drugs (73.4% and 60.4% respectively). In each setting, the majority of patients were prescribed one or two off-label drugs. The maximum number of off-label drugs was 11, prescribed to one inpatient. Of the 356 patients that were not prescribed any off-label drugs, 321 were prescribed licensed drugs and 35 were prescribed unlicensed drugs. Some patients that were prescribed off-label drugs were also prescribed unlicensed drugs. The number of patients prescribed both off-label and unlicensed drugs was 24 (19 males and five females - Table 3.17).

Table 3.21 - Number of drugs prescribed per person in each setting, including licensed drugs as well as off-label and unlicensed

Drugs per person	Inpatient (n = 254)		Outpatient (n = 380)		Emergency (n = 403)		Total (n = 1037)
	n		n		n		
0 (%)	12	3.6	173	51.2	153	45.3	338
1 (%)	20	9.3	80	37.2	115	53.5	215
2 (%)	21	15.8	62	46.6	50	37.6	133
3 (%)	28	31.8	24	27.3	36	40.9	88
4 (%)	34	49.3	15	21.7	20	29.0	69
5 (%)	20	60.6	8	24.2	5	15.2	33
6 (%)	30	61.2	11	22.4	8	16.3	49
7 (%)	16	76.2	3	14.3	2	9.5	21
8 (%)	18	85.7	2	9.5	1	4.8	21
9 (%)	15	93.8	0	0.0	1	6.2	16
10 (%)	9	75.0	0	0.0	3	25.0	12
11 (%)	9	75.0	1	8.3	2	16.7	12
12 (%)	6	60.0	1	10.0	3	30.0	10
13 (%)	3	100.0	0	0.0	0	0.0	3
14 (%)	2	100.0	0	0.0	0	0.0	2
15 (%)	1	50.0	0	0.0	1	50.0	2
16 (%)	2	40.0	0	0.0	3	60.0	5
19 (%)	1	100.0	0	0.0	0	0.0	1
21 (%)	7	100.0	0	0.0	0	0.0	7

($p < 0.0001$)

Table 3.22 - Number of patients prescribed different numbers of off-label drugs in each setting

Off-label drugs per person	Inpatient (n = 242)		Outpatient (n = 207)		Emergency (n = 250)		Total number (n = 699)
	n	% of inpatients	n	% of outpatients	n	% of emergency	
0	53	21.9	152	73.4	151	60.4	356
1	64	26.5	35	16.9	66	26.4	165
2	58	24.0	15	7.3	19	7.6	92
3	39	16.1	2	1.0	3	1.2	44
4	17	7.0	2	1.0	6	2.4	25
5	5	2.1	1	0.5	3	1.2	9
6	4	1.7	0	0.0	2	0.8	6
8	1	0.4	0	0.0	0	0.0	1
11	1	0.4	0	0.0	0	0.0	1

$p < 0.0001$

Table 3.23 shows the average age of patients prescribed no drugs, licensed or off-label and unlicensed drugs. The average age of patients that were not prescribed any drugs was 6.36 (± 4.89) years (median age = 5.59). The number of licensed drugs prescribed ranged from one to 12 and the average age of patients prescribed licensed drugs was 7.54 (± 5.52) years (median age = 6.97). The number of off-label drugs prescribed ranged from zero to eleven and the number of unlicensed drugs ranged from zero to three. Patients that were prescribed off-label or unlicensed drugs may also have been prescribed licensed drugs so the overall number of drugs they were prescribed ranged from one to 21 drugs and their average age was 6.01 (± 5.07)(median age = 4.72).

Table 3.23 - Average age of patients prescribed no drugs, licensed, off-label or unlicensed drugs

Type of Drug	Average age (± 1 SD)	Range of drugs prescribed	Range of off-label drugs per person	Range of unlicensed drugs per person
No drugs (n = 338)	6.36 (4.89) (median = 5.59)	0	0	0
Licensed drugs (n = 321)	7.54 (5.52) (median = 6.97)	1 - 12	0	0
Off-label or unlicensed drugs (n = 378)	6.01 (5.07) (median = 4.72)	1 - 21	0 - 11	0 - 3

Table 3.24 summarises the maximum number of drugs prescribed to various age groups in Emergency Department admissions, inpatients and outpatients. The maximum number of drugs prescribed to individual patients was 21 which were prescribed to inpatients in all age groups except infants (aged 28 days to 23 months). The maximum number of drugs prescribed to infants (aged 28 days to 23 months) was fourteen. For outpatient, the maximum number of drugs prescribed was twelve (prescribed to children aged two to 11 years) and in the Emergency Department, the maximum number of drugs prescribed was sixteen, for both infants (aged 28 days to 23 months) and children (aged two to 11 years).

Table 3.24 - Maximum number of drugs prescribed per patient, including all drugs, off-label and unlicensed drugs in various settings according to age group

Patient status	Age group	Maximum number of drugs prescribed per patient		
		All drugs	Off-label	Unlicensed
Inpatient	**0 - 27 days** (n = 12)	21	6	1
(n = 254)	**28 days - 23 months** (n = 67)	14	6	1
	2 - 11 years (n = 122)	21	11	2
	12 - 18 years (n = 53)	21	6	1
Outpatient	**0 - 27 days** (n = 2)	4	2	0
(n = 380)	**28 days - 23 months** (n = 78)	8	4	2
	2 - 11 years (n = 202)	12	5	1
	12 - 18 years (n = 98)	11	2	2
Emergency	**0 - 27 days** (n = 6)	3	1	0
(n = 403)	**28 days - 23 months** (n = 133)	16	6	3
	2 - 11 years (n = 200)	16	5	2
	12 - 18 years (n = 64)	15	4	0

The maximum number of off-label drugs was eleven, prescribed to inpatients children (aged two to 11 years). In the outpatient setting, the maximum number of off-label drugs prescribed was five, prescribed to children (aged two to 11 years) and in the Emergency Department it was six, prescribed to infants (aged 28 days to 23 months). The lowest maximum was one drug prescribed to neonates in the Emergency Department.

The maximum number of unlicensed drugs was three, prescribed in the Emergency Department to infants (aged 28 days to 23 months). A maximum of two unlicensed drugs was prescribed to inpatient and Emergency Department children (aged two to 11 years) and to outpatient infants (aged 28 days to 23 months) and adolescents (aged 12 to 18 years).

3.6 Details of off-label and unlicensed drug usage

Of the 2654 drugs recorded in this study, the number of drugs prescribed in each setting is shown in Table 3.25. More drugs were prescribed to inpatients (1494) than outpatients (502) or Emergency Department patients (658). In considering the number of drugs prescribed in each setting, a higher percentage of off-label drugs were prescribed to inpatients (29.0%) and Emergency Department patients (25.0%). The least number of off-label drugs were prescribed to outpatients (16.7%). However, in considering only the 681 off-label drugs, the highest percentage (63.6%) were prescribed to inpatients and the least (12.3%) were prescribed to outpatients. The differences in the categories of drugs prescribed in each setting were significant ($p < 0.0001$).

Table 3.25 - Drug classifications prescribed in each setting

Setting (n = 2654)	**Licensed** (n = 1905)		**Off-label** (n = 681)		**Unlicensed** (n = 68)	
Inpatient (n = 1494) (%)	1036	69.3	433	29	25	1.7
Outpatient (n = 502) (%)	398	79.3	84	16.7	20	4
Emergency (n = 658) (%)	471	71.6	164	25	23	3.5

($p < 0.0001$)

For each setting, the gender distribution was obtained to determine whether there were differences in off-label and unlicensed prescribing in male and female patients (Table 3.26). Licensed, off-label and unlicensed prescribing trends were similar for male and female inpatients. Female outpatients were prescribed more licensed and unlicensed drugs than males (81.5% and 5.9% respectively compared to 77.8% and 2.7% respectively for males). Male outpatients were prescribed more off-label drugs than female outpatients (19.5% compared to 12.7% for females). Licensed prescribing for male and female Emergency Department patients were similar (70.2% for males and 73.5% for females) and off-label prescribing was also similar for both sexes (25.1% and 24.7% respectively). There was a higher percent of unlicensed prescriptions for Emergency Department males (4.7% compared to 1.8% for females).

Table 3.26 - Gender distribution showing the number of licensed, off-label and unlicensed drugs prescribed in each setting

Setting (n = 2654)	Gender	Drugs Prescribed					
		Licensed (n = 1905)		Off-label (n = 681)		Unlicensed (n = 68)	
Inpatient (n = 1494)	**Male** (n = 1009) (%)	697	69.1	296	29.3	16	1.6
	Female (n = 485) (%)	339	69.9	137	28.2	9	1.9
Outpatient (n = 502)	**Male** (n = 297) (%)	231	77.8	58	19.5	8	2.7
	Female (n = 205) (%)	167	81.5	26	12.7	12	5.9
Emergency (n = 658)	**Male** (n = 379) (%)	266	70.2	95	25.1	18	4.7
	Female (n = 279) (%)	205	73.5	69	24.7	5	1.8

Tables 3.27, 3.28 and 3.29 show off-label and unlicensed drugs prescribed to male and female patients in each setting. The most frequently prescribed off-label drug for inpatients was ondansetron (Table 3.27), for outpatients it was midazolam (Table 3.28) and for Emergency Department patients it was Painstop Day® (Table 3.29). The most frequently prescribed unlicensed drugs for inpatients were both dexamethasone and adrenaline (Table 3.27), for outpatients it was dilacaine (Table 3.28) and for Emergency Department patients it was dexamethasone (Table 3.29)

Table 3.27 - Off-label and unlicensed drugs prescribed to inpatients

INPATIENTS
Off-Label
(n = 296 males, 137 females)

Drug	Male	Female	Drug	Male	Female	Drug	Male	Female	Drug	Male	Female
Aciclovir	2	0	Hydralazine	1	0	Nifedipine	1	0	Temazepam	1	3
Alfentanil	1	0	Hydrocortisone	1	0	Omeprazole	3	1	Terbinafine	1	0
Alteplase	2	0	Hyoscine butylbromide	1	0	Ondansetron	52	25	Ticarcillin with clavulanic acid	6	4
Amoxicillin	10	3	Ibuprofen	0	1	Oxybutynin	1	0	Tobramycin	3	1
Aprepitant	3	0	Interferon beta	1	0	Oxycodone	25	15	Topotecan	1	1
Atorvastatin	0	1	Ipratropium	2	2	Painstop®	20	17	Tropisetron	1	0
Amoxicillin with clavulanic acid	2	1	Lactulose	1	0	Painstop night®	3	1	Vancomycin	4	0
Benzylpenicillin	1	0	Lamotrigine	0	1	Panadeine forte®	1	0	Vigabatrin	0	1
Calcium carbonate	0	1	Lansoprazole	0	1	Pantoprazole	1	0	Vitabdeck®	0	1
Chloral hydrate	2	1	Levetiracetam	0	1	Paracetamol	26	9	**Unlicensed** (n = 16 males, 9 females)		
Chloramphenicol	2	0	Lignocaine	1	0	Parachoc®	1	0	Adrenaline	4	0
Ciprofloxacin	1	0	Lisinopril	0	1	Parecoxib	1	1	Carnitine	0	2
Clobazam	0	1	Lorazepam	5	1	Pizotifen	0	1	Cephazolin	1	0
Clonidine	6	3	Losartan	0	1	Potassium chloride	1	0	Cisretinoic acid	1	0
Codeine	7	3	Melatonin	0	1	Praziquantel	1	0	Dexamethasone	4	0
Dexamethasone	3	1	Meropenem	1	0	Pregabalin	0	1	Dilacaine	1	1
Dopamine	2	0	Methotrexate	1	0	Promethazine	3	0	Gonadorelin	0	2
Escitalopram	1	0	Metoclopramide	7	4	Propofol	6	0	Magnesium chloride	1	0
Fentanyl	8	2	Metronidazole	0	1	Quetiapine	1	1	Metolazone	0	1
Flucloxacillin	7	3	Microlax®	1	1	Ranitidine	3	0	Picibanil	1	0
Fluorouracil	1	0	Midazolam	15	5	Salbutamol	18	7	Potassium chloride	1	0
Fluoxetine	0	1	Mirtazapine	0	1	Sertraline	0	1	Sodium bicarbonate	1	0
Gabapentin	0	2	Morphine	2	1	Sildenafil	2	0	Sodium chloride	1	2
Gentamicin	6	1	Natalizumab	1	0	SOOV IT®	1	0	Tocilizumab	0	1

Table 3.28 - Off-label and unlicensed drugs prescribed to outpatients

OUTPATIENTS
Off-Label
(n = 58 males, 26 females)

Drug	Male	Female	Drug	Male	Female	Drug	Male	Female	Drug	Male	Female
Aciclovir	1	0	Eformoterol/ budesonide	0	1	Minoxidil	0	1	Valaciclovir	1	0
Amitriptyline	0	1	Epipen jr®	1	0	Nifedipine	1	0	Valganciclovir	1	0
Amlodipine	1	0	Fentanyl	2	0	Nitrazepam	0	1	Vitabdeck®	1	0
Amoxicillin	1	2	Fluorometholone	1	0	Octreotide	0	1	Xalacom®	0	1
Azithromycin	1	0	Fluoxetine	1	1	Ofloxacin	1	0		3	1
Betamethasone	1	1	Glyceryl trinitrate	1	0	Omeprazole	1	1	**Unlicensed**		
Betaxolol	1	0	Hydralazine	1	0	Ondansetron	3	0	(n = 8 males, 12 females)		
Brimonidine	1	0	Hydroxyurea	1	0	Painstop®	2	2	Aspirin	1	0
Brinzolamide	1	0	Infliximab	1	0	Paracetamol	2	0	Azathioprine	2	0
Captopril	1	0	Lactulose	1	1	Risperidone	0	1	Carnitine	0	1
Carbimazole	1	0	Lansoprazole	1	0	Salbutamol	2	0	Dilacaine	3	7
Cephalexin	0	1	Latanoprost	1	0	Sertraline	0	1	Domperidone	0	1
Chloramphenicol	1	0	Levetiracetam	1	0	Solifenacin	1	1	Propranolol	1	0
Clobazam	2	0	Loperamide	1	0	Ticarcillin with clavulanic acid	1	0	Salicylic acid/ cetylpyridium chloride	0	1
Clonidine	1	2	Loratadine	0	1	Timolol	1	0	Sodium chloride	1	0
Darbepoetin alfa	1	0	Methotrexate	0	1	Tobramycin	2	1	Tacrolimus	0	1
Dexamethasone	2	1	Metoclopramide	1	0	Tolterodine	0	1	Trichloracetic acid paste	0	1
Dopamine	1	0	Midazolam	4	1	Tropicamide	1	0			

Table 3.29 - Off-label and unlicensed drugs prescribed to Emergency Department patients

EMERGENCY PATIENTS **Off-Label** (n = 95 males, 69 females)											
Drug	**Male**	**Female**	**Drug**	**Male**	**Female**	**Drug**	**Male**	**Female**	**Drug**	**Male**	**Female**
Aciclovir	2	0	Gentamicin	1	0	Olanzapine	1	1	Teicoplanin	0	1
Adrenaline	1	0	Ibuprofen	0	3	Omeprazole	1	3	Temazepam	0	1
Alfentanil	1	0	Ipratropium	6	2	Ondansetron	8	6	Ticarcillin with clavulanic acid	7	1
Amoxicillin	0	2	Ketamine	1	0	Oxycodone	4	5	Vancomycin	1	0
			Leuprorelin acetate	0	1	Painstop Day®	14	16	**Unlicensed** (n = 18 males, 5 females)		
Benzylpenicillin	1	0									
Cephalexin	0	1	Loratadine	2	0	Painstop night®	0	1	Adrenaline	3	0
Chloramphenicol	1	0	Lorazepam	1	0	Pantoprazole	1	0	Aspirin	1	0
Clonidine	0	1	Metronidazole	1	1	Paracetamol	5	6	Dexamethasone	11	5
Fentanyl	6	3	Midazolam	3	1	Propofol	0	1	Domperidone	1	0
Flucloxacillin	5	3	Montelukast	1	0	Quetiapine	2	0	Potassium Chloride	1	0
Fluoxetine	1	0	Mupirocin	2	0	Salbutamol	15	9	Tinidazole	1	0

To determine differences in prescribing trends with age, the distribution of licensed, off-label and unlicensed drugs for the four age groups is shown in Table 3.30. The highest percentages of licensed drugs were prescribed to children aged two to 11 years (46.7%). This was also the age group prescribed the highest percentage of off-label drugs (56.8%). The highest percentage of unlicensed prescribing was in infants aged 28 day to 23 months (52.9%). The smallest percentage of licensed prescribing was in neonates aged zero to 27 days (3.3%). This age group also had the smallest percentage of off-label and unlicensed prescribed drugs (4.4% and 1.5% respectively).

Table 3.30 - Distribution of the type of drug prescribed to the various age groups

Type of Drug	Age group of patients							
	0 - 27 days (n = 94)		28 days - 23 months (n = 533)		2 - 11 years (n = 1302)		12 - 18 years (n = 725)	
Licensed (n = 1905) (%)	63	3.3	333	17.5	890	46.7	619	32.5
Off-label (n = 681) (%)	30	4.4	164	24.1	387	56.8	100	14.7
Unlicensed (n = 68) (%)	1	1.5	36	52.9	25	36.8	6	8.8

When all of the 2654 drugs prescribed were categorised according to their ATC code and separated into licensed, off-label and unlicensed drugs (Table 3.31), the majority of licensed and off-label drugs were classified into the nervous system (n = 1034; 39.0%). There were no unlicensed drugs in this category. The categories with the highest percentage of unlicensed drugs were systemic hormonal preparations excluding sex hormones (n = 22; 14.4%) and sensory organ drugs (n = 13; 13.7%).

Table 3.31 - Frequency of licensed, off-label and unlicensed drugs prescribed in each ATC category.

ATC	Licensed (n = 1905)		Off-label (n = 681)		Unlicensed (n = 68)	
Alimentary tract and metabolism (n = 408) (%)	258	63.2	139	34.1	11	2.7
Blood and blood forming organs (n = 34) (%)	28	82.4	3	8.8	3	8.8
Cardiovascular system (n = 69) (%)	37	53.6	28	40.6	4	5.8
Dermatologicals (n = 111) (%)	101	91.0	7	6.3	3	2.7
Genito-urinary system and sex hormones (n = 19) (%)	10	52.6	7	36.8	2	10.5
Systemic hormonal preparations excl sex hormones (n = 154) (%)	129	83.8	3	1.9	22	14.3
Anti-infectives for systemic use (n = 400) (%)	302	75.5	97	24.3	1	0.2
Antineoplastics and immunomodulating agents (n = 42) (%)	28	66.7	9	21.4	5	11.9
Musculo-skeletal system (n = 73) (%)	71	97.3	2	2.7	0	0.0
Nervous system (n = 1034) (%)	739	71.5	295	28.5	0	0.0
Antiparasitic products, insecticides and repellent (n = 5) (%)	4	80.0	1	20.0	0	0.0
Respiratory system (n = 180) (%)	106	58.9	71	39.4	3	1.7
Sensory organs (n = 95) (%)	63	66.3	19	20.0	13	13.7
Various (n = 30) (%)	29	96.7	0	0.0	1	3.3

Table 3.32 lists the thirty most commonly prescribed drugs overall in descending order, indicating whether they were prescribed in a licensed, off-label or unlicensed manner. The ten most commonly prescribed drugs were paracetamol, ibuprofen, ondansetron, Painstop Day®, morphine, oxycodone, amoxicillin, dexamethasone, salbutamol and prednisolone.

Table 3.32 shows that of the ten most commonly prescribed drugs overall, several were prescribed in an off-label manner more frequently than in a licensed manner including ondansetron (74.6%), Painstop Day® (88.8%), oxycodone (66.2%) and salbutamol (87.9%). Other drugs that were prescribed in an off-label manner more frequently than in a licensed manner included fentanyl (53.8%), midazolam (93.5%), ticarcillin/ clavulanic acid (Timentin®) (95.0%) and omeprazole (55.6%). Some drugs, including prednisolone, Emla® cream, hydrocortisone, NovoRapid® insulin, Panadeine® and ceftriaxone, were not prescribed in either an off-label or unlicensed manner.

Dexamethasone, which is marketed in a number of dosage forms including tablets, injection and eye drops, was prescribed in a licensed, off-label and unlicensed manner. In the six cases where the drug was used in an off-label manner, eye drops were administered to patients despite the safety and efficacy in paediatric patients not having been established. All twenty unlicensed uses of dexamethasone were due to reformulation.

The ten most commonly prescribed drugs to different age groups are shown in Table 3.33 (including licensed, unlicensed and off-label drugs). Prescribing trends for different age groups varied, especially drugs prescribed to neonates (aged zero to 27 days) since these included mainly anti-infectives such as amoxicillin, gentamicin, cefotaxime, nystatin, aciclovir, amoxicillin with clavulanic acid (Augmentin Duo®) and vancomycin. The most commonly prescribed drugs to infants (aged 27 days to 23 months) included analgesics (paracetamol and ibuprofen), respiratory drugs (salbutamol) and anti-infectives (amoxicillin, flucloxacillin and amoxicillin/ clavulanic acid).

Table 3.32 - The 30 most common drugs prescribed overall.

Drug	Licensed		Off-label		Unlicensed		Total
	n	%	n	%	n	%	
Paracetamol	265	84.7	48	15.3	0	0.0	313
Ibuprofen	196	98	4	2.0	0	0.0	200
Ondansetron	32	25.4	94	74.6	0	0.0	126
Painstop Day® (paracetamol/ codeine)	9	11.2	71	88.8	0	0.0	80
Morphine	76	96.2	3	3.8	0	0.0	79
Oxycodone	25	33.8	49	66.2	0	0.0	74
Amoxicillin	41	68.3	18	31.7	0	0.0	59
Dexamethasone	32	55.2	6	10.3	20	34.5	58
Salbutamol	7	12.1	51	87.9	0	0.0	58
Prednisolone	48	100	0	0.0	0	0.0	48
Flucloxacillin	23	56.1	18	43.9	0	0.0	41
Fentanyl	18	46.2	21	53.8	0	0.0	39
Augmentin duo® (amoxicilin/ clavulanic acid)	30	90.9	3	9.1	0	0.0	33
Midazolam	2	6.5	29	93.5	0	0.0	31
Propofol	22	75.9	7	24.1	0	0.0	29
Emla® (lignocaine/ prilocaine)	26	100	0	0.0	0	0.0	26
Loratadine	23	88.5	3	11.5	0	0.0	26
Metoclopramide	14	53.8	12	46.2	0	0.0	26
Chloramphenicol	18	81.8	4	18.2	0	0.0	22
Cephalexin	19	90.5	2	9.5	0	0.0	21
Gentamicin	13	61.9	8	38.1	0	0.0	21
Lactulose	18	85.7	3	14.3	0	0.0	21
Panadeine forte	20	95.2	1	4.8	0	0.0	21
Hydrocortisone	20	100	0	0.0	0	0.0	20
NovoRapid® (insulin aspart)	20	100	0	0.0	0	0.0	20
Timentin® (ticarcillin/ clavulanic acid)	1	5.0	19	95.0	0	0.0	20
Metronidazole	16	84.2	3	15.8	0	0.0	19
Panadeine® (paracetamol/ codeine)	19	100	0	0.0	0	0.0	19
Omeprazole	8	44.4	10	55.6	0	0.0	18
Ceftriaxone	16	100	0	0.0	0	0.0	16

Table 3.33 - The ten most common drugs, including licensed, off-label or unlicensed drugs, to various age groups.

Drugs prescribed for 0 - 27 days (n = 94 drugs)			Drugs prescribed for 27 days - 23 months (n = 533 drugs)			Drugs prescribed for 2 - 11 years (n = 1302 drugs)			Drugs prescribed for 12 - 18 years (n = 725 drugs)		
Drugs	**Frequency**	**%**	**Drugs**	**Frequency**	**%**	**Drugs**	**Frequency**	**%**	**Drugs**	**Frequency**	**%**
Amoxicillin	12	12.8	Paracetamol	91	17.1	Paracetamol	163	12.5	Paracetamol	51	7
Gentamicin	10	10.6	Ibuprofen	46	8.6	Ibuprofen	108	8.3	Ibuprofen	45	6.2
Paracetamol	8	8.5	Salbutamol	26	4.9	Ondansetron	79	6.1	Ondansetron	33	4.6
Cefotaxime	4	4.3	Dexamethasone	17	3.2	Painstop Day® (paracetamol/ codeine)	65	5	Oxycodone	30	4.1
Nystatin	4	4.4	Amoxicillin	14	2.6	Morphine	43	3.3	Morphine	23	3.2
Aciclovir	3	3.2	Flucloxacillin	14	2.6	Oxycodone	40	3.1	Panadeine Forte® (paracetamol/ codeine)	18	2.5
Amoxicillin/ clavulanic acid	3	3.2	Ondansetron	14	2.6	Dexamethasone	32	2.5	Panadeine® (paracetamol/ codeine)	17	2.3
Morphine	3	3.2	Prednisolone	14	2.6	Amoxicillin	29	2.2	Fentanyl	12	1.7
Omeprazole	3	3.2	Dilacaine	11	2.1	Fentanyl	26	2.0	Prednisolone	11	1.5
Vancomycin	3	3.2	Amoxicillin/ clavulanic acid	10	1.9	Salbutamol	26	2.0	Glargine insulin	10	1.4

Children aged two to 11 years were prescribed mainly analgesics (paracetamol, ibuprofen, Painstop Day®, morphine, oxycodone and fentanyl) and alimentary tract drugs (ondansetron). Adolescents (aged 12 to 18 years) were also prescribed mainly analgesics and alimentary tract drugs but instead of Painstop Day®, they were prescribed Panadeine Forte® and Panadeine®.

Considering only drugs prescribed in an off-label manner, the twenty most frequently prescribed off-label drugs are shown in Table 3.34. Off-label drugs shown in Table 3.34 include the alimentary tract drugs ondansetron, nervous system drugs including Painstop Day®, oxycodone, paracetamol, midazolam and fentanyl, the respiratory system drug salbutamol, as well as the anti-infectives ticarcillin with clavulanic acid, amoxicillin and flucloxacillin. Ondansetron was the most frequently prescribed off-label drug.

The ten most commonly prescribed off-label drugs prescribed to the various age groups are shown in Table 3.35. Off-label prescribing trends varied for the different age groups. Six of the ten most common drugs prescribed to neonates (aged zero to 27 days) were anti-infectives including amoxicillin, gentamicin, aciclovir, amoxicillin with clavulanic acid (Augmentin Duo®), meropenem and metronidazole. The most commonly prescribed drug to infants aged 27 days to 23 months was the respiratory drug salbutamol. Other drugs included analgesics (paracetamol, Painstop Day® and codeine), alimentary tract drugs (ondansetron and omeprazole), anti-infectives (amoxicillin and flucloxacillin) and other drugs affecting the nervous system (midazolam and propofol). The most commonly prescribed drug to children aged two to 11 years was Painstop Day®. Other analgesics included oxycodone, paracetamol and fentanyl. The second most common drug prescribed to children aged two to 11 years was ondansetron. Ondansetron was the most common drug prescribed to adolescents aged 12 to 18 years. Other drugs included drugs affecting the nervous system (fentanyl, lorazepam, oxycodone, temazepam, midazolam and quetiapine) and anti-infectives (ticarcillin/ clavulanic acid and tobramycin).

Table 3.34 - The twenty most common off-label drugs and their frequencies

Off-label drug	Frequency	Percent	ATC Category
Ondansetron	94	13.8	Alimentary Tract
Painstop Day®	71	10.4	Nervous system
Salbutamol	51	7.5	Respiratory System
Oxycodone	49	7.2	Nervous system
Paracetamol	48	7.1	Nervous system
Midazolam	29	4.3	Nervous system
Fentanyl	21	3.1	Nervous system
Ticarcillin/ clavulanic acid	19	2.8	Anti-infective
Amoxicillin	18	2.6	Anti-infective
Flucloxacillin	18	2.6	Anti-infective
Clonidine	13	1.9	Cardiovascular System
Ipratropium	12	1.8	Respiratory System
Metoclopramide	12	1.8	Alimentary Tract
Codeine	10	1.5	Nervous system
Omeprazole	10	1.5	Alimentary Tract
Gentamicin	8	1.2	Anti-infective
Lorazepam	7	1.0	Nervous system
Propofol	7	1.0	Nervous system
Tobramycin	7	1.0	Nervous system
Dexamethasone	6	0.9	Sensory Organs

Table 3.36 lists all off-label drugs prescribed in each ATC category and shows the frequency of each drug.

Table 3.35 - The ten most common off-label drugs prescribed to different age groups

Drugs prescribed for 0 - 27 days (n = 94 drugs)			Drugs prescribed for 28 days - 23 months (n = 533 drugs)			Drugs prescribed for 2 - 11 years (n = 1302 drugs)			Drugs prescribed for 12 - 18 years (n = 725 drugs)		
Drugs	**Freq**	**%**	**Drugs**	**Freq**	**%**	**Drugs**	**Freq**	**%**	**Drugs**	**Freq**	**%**
Amoxicillin	9	30.0	Salbutamol	25	15.2	Painstop Day®	60	15.6	Ondansetron	23	23.0
Gentamicin	4	13.3	Ondansetron	14	8.5	Ondansetron	57	14.7	Fentanyl	7	7.0
Aciclovir	3	10.0	Paracetamol	13	7.9	Oxycodone	40	10.3	Lorazepam	5	5.0
Omeprazole	3	10.0	Painstop Day®	10	6.1	Paracetamol	34	8.8	Oxycodone	5	5.0
Augmentin Duo®	2	6.7	Amoxicillin	7	4.3	Salbutamol	23	5.9	Temazepam	5	5.0
Dopamine	2	6.7	Flucloxacillin	7	4.3	Midazolam	16	4.1	Ticarcillin/ clavulanic acid	5	5.0
Midazolam	2	6.7	Midazolam	7	4.3	Fentanyl	13	3.4	Fluoxetine	4	4.0
Hydrocortisone	1	3.3	Omeprazole	7	4.3	Clonidine	11	2.8	Midazolam	4	4.0
Meropenem	1	3.3	Codeine	6	3.7	Flucloxacillin	11	2.8	Quetiapine	4	4.0
Metronidazole	1	3.3	Propofol	5	3.1	Metoclopramide	10	2.6	Tobramycin	4	4.0

Table 3.36 - Details of off-label drugs prescribed in each ATC category with their respective frequencies

Alimentary tract and metabolism (n = 139)		**Genito-urinary system and sex hormones** (n = 7)		**Nervous system** (n = 295)		**Antineoplastic and immunomodulating agents** (n = 9)	
Ondansetron	94	Sildenafil	2	Painstop Day®	71	Methotrexate	2
Metoclopramide	12	Solifenacin	2	Oxycodone	49	Topotecan	2
Omeprazole	10	Leuprorelin acetate	1	Paracetamol	48	5-fluorouracil	1
Aprepitant	3	Oxybutynin	1	Midazolam	29	Hydroxyurea	1
Lactulose	3	Tolterodine	1	Fentanyl	21	Infliximab	1
Ranitidine	3	**Dermatologicals** (n = 7)		Codeine	10	Interferon beta	1
Lansoprazole	2	Mupirocin	2	Lorazepam	7	Natalizumab	1
Microlax®	2	Betamethasone	2	Propofol	7	**Respiratory System** (n = 71)	
Pantoprazole	2	SOOV®	1	Painstop Night	5	Salbutamol	51
Vitabdeck	2	Glyceryl trinitrate	1	Temazepam	5	Ipratropium	12
Calcium carbonate	1	Minoxidil	1	Fluoxetine	4	Loratidine	3
Hyoscine butylbromide	1	**Anti-infective** (n = 97)		Ibuprofen	4	Promethazine	3
Loperamide	1	Ticarcillin/ clavulanic acid	19	Quetiapine	4	Eformoterol/ budesonide	1
Paraffin liquid (Parachoc®)	1	Flucloxacillin	18	Chloral hydrate	3	Montelukast	1
Potassium chloride	1	Amoxicillin	18	Clobazam	3	**Sensory Organs** (n = 19)	
Tropisetron	1	Gentamicin	8	Morphine	3	Dexamethasone	6
Blood and blood forming organs (n = 3)		Tobramycin	7	Alfentanil	2	Chloramphenicol	4
Alteplase	2	Aciclovir	5	Gabapentin	2	Betaxolol	1
Darbepoetin alfa	1	Vancomycin	5	Levetiracetam	2	Brimonidine	1
Cardiovascular System (n = 28)		Amoxicillin/ clavulanic acid	3	Olanzapine	2	Brinzolamide	1
Clonidine	13	Metronidazole	3	Sertraline	2	Fluorometholone	1
Dopamine	3	Benzylpenicillin	2	Amitriptyline	1	Latanoprost	1
Hydralazine	2	Cephalexin	2	Escitalopram	1	Latanoprost/ timolol	1
Nifedipine	2	Azithromycin	1	Ketamine	1	Ofloxacin	1
Adrenaline	1	Ciprofloxacin	1	Lamotrigine	1	Timolol	1
Amlodipine	1	Meropenem	1	Melatonin	1	Tropicamide	1
Atorvastatin	1	Teicoplanin	1	Mirtazapine	1	**Systemic hormonal preparations, excl sex hormones** (n = 3)	
Captopril	1	Terbinafine	1	Nitrazepam	1	Carbimazole	1
Epipen junior	1	Valaciclovir	1	Paracetamol/ codeine	1	Hydrocortisone	1
Lignocaine	1	Valganciclovir	1	Pizotifen	1	Octreotide	1
Lisinopril	1	**Musculoskeletal system** (n = 2)		Pregabalin	1	**Antiparasitic products, insecticides and repellent** (n = 1)	
Losartan	1	Parecoxib	2	Risperidone	1		
				Vigabatrin	1	Praziquantil	1

As outlined in Chapter 2, a hierarchical approach was used in assigning reasons for off-label prescribing. This was done so that each drug was assigned only to one single category. The order of allocations was age, indication, route of administration and dose (including inappropriate frequency). Therefore, a drug off-label for dose and age would be classified as off-label for age. Similarly, for a drug administered at an inappropriate frequency where the age was within the marketing authorisation, the reason for off-label prescribing would be recorded as dosage. However, where a drug not marketed for a particular age group was administered at an inappropriate frequency, the reason for off-label prescribing would be due to age. Hence, there may have been more dosages which were off-label but where age as the primary factor may have rendered it off-label, then the dosage was not evaluated. The same applied to the other reasons.

Table 3.37 shows that the most common reasons for off-label prescribing were due to age and dosage (43.2% and 47.4% respectively). When considering that some drugs, where dose was a factor, were likely to be combined with those where age was a factor, indicates that dosage was clearly the primary factor leading to off-label prescribing. The least common reason for off-label prescribing was due to indication.

Table 3.37 - Reasons for off-label prescribing showing the hierarchical classification used

Reason for off-label prescribing	**Frequency** (n = 681)	**Percentage**
Age	294	43.2
Indication	29	4.3
Route of administration	35	5.1
Dosage (including inappropriate frequency)	323	47.4

When the reasons for off-label prescribing were determined for each ATC code (Table 3.38), in the alimentary system the majority of drugs were off-label due to dosage (51.8%). With respect to the nervous system, a large percentage of drugs were off-label due to age (44.4%) and dosage (44.1%).

The most commonly prescribed unlicensed drugs were dexamethasone (20/ 68), dilacaine (12/ 68) and adrenaline (7/ 68). All unlicensed drugs were categorised into the appropriate ATC category (Table 3.39). The ATC category with the majority of unlicensed drugs were systemic hormonal preparations excluding sex hormones (n = 20, 29.4%) and sensory organ drugs (n = 13, 19.1%). The most commonly prescribed unlicensed systemic hormonal preparation excluding sex hormones was dexamethasone and the most commonly prescribed unlicensed sensory organ drug was dilacaine. Dexamethasone was reformulated from tablets into a liquid dosage form suitable for administration. Dilacaine mydriatic eye drops were formulated at PMH since no commercial preparation was available. Each 1 mL of dilacaine eye drops contained proxymetacaine 1.25 mg, cyclopentolate 2.5 mg, tropicamide 2.5 mg and phenylephrine 25 mg. The eye drops were intended to be instilled into the eye one hour prior to examination and the formulation was for individual patient use only. There were no unlicensed drugs in a number of ATC categories including the musculoskeletal system, nervous system and antiparasitic products, insecticides and repellent.

Table 3.40 shows the most commonly prescribed unlicensed drugs to different age groups. The only unlicensed drug prescribed to a neonate aged zero to 27 days was cephazolin which was formulated as an eye drop. Only six unlicensed drugs were prescribed to adolescents aged 12 to 18 years which included two topical preparations for eczema.

Table 3.38 - Reasons for off-label prescribing in each ATC category

Off-label	Age (n = 294)	Indication (n = 29)	Route of admin. (n = 35)	Dosage (n = 323)
Alimentary tract (n = 139) (%)	54 (38.9)	13 (9.4)	0 (0.0)	72 (51.8)
Blood and blood forming products (n = 3) (%)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular system (n = 28) (%)	24 (85.7)	2 (7.1)	2 (7.1)	0 (0.0)
Dermatologicals (n = 7) (%)	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genitourinary system & sex hormones (n = 7) (%)	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic hormonal preparations (n = 3) (%)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-infective (n = 97) (%)	32 (33.0)	3 (3.1)	4 (4.1)	58 (59.8)
Antineoplastics (n = 9) (%)	5 (55.6)	2 (22.2)	0 (0.0)	2 (22.2)
Musculo-skeletal system (n = 2) (%)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system (n = 295) (%)	131 (44.4)	5 (1.7)	29 (9.8)	130 (44.1)
Antiparasitic products, insecticides and repellent (n = 1) (%)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory system (n = 71) (%)	10 (14.1)	0 (0.0)	0 (0.0)	61 (85.9)
Sensory organs (n = 19) (%)	15 (78.9)	4 (21.1)	0 (0.0)	0 (0.0)

Table 3.39 - Listing of the 68 unlicensed drugs in appropriate ATC categories

ATC category	Drugs	Frequency (n = 68)	%
Alimentary tract (n = 11) (%)	Sodium chloride	4	36.4
	Carnitine	3	27.3
	Domperidone	2	18.2
	Magnesium chloride	1	9.1
	Potassium chloride	1	9.1
Blood and blood forming products (n = 3) (%)	Aspirin	2	66.7
	Sodium bicarbonate	1	33.3
Cardiovascular system (n = 4) (%)	Adrenaline	2	50.0
	Metolazone	1	25.0
	Propranolol	1	25.0
Dermatologicals (n = 3) (%)	Sal acid/ cetylpyridinium	1	33.3
	Tacrolimus	1	33.3
	Trichloracetic acid paste	1	33.3
Genitourinary system & sex hormones (n = 2) (%)	Gonadorelin	2	100.0
Systemic hormonal preparations (n = 20) (%)	Dexamethasone	20	100.0
Anti-infective (n = 1) (%)	Tinidazole	1	100.0
Antineoplastics and immunomodulating agents (n = 5) (%)	Azathioprine	2	40.0
	Picibanil (OK 432)	1	20.0
	Cisretinoic acid	1	20.0
	Tocilizumab	1	20.0
Respiratory system (n = 5) (%)	Adrenaline	5	100.0
Sensory organs (n = 13) (%)	Dilacaine	12	92.3
	Cephazolin	1	7.7
Various (n = 1) (%)	Potassium chloride	1	100.0

Table 3.40 - The ten most commonly prescribed unlicensed drugs (where available) prescribed to various age groups

Drugs prescribed for 0 - 27 days (n = 94 drugs)			**Drugs prescribed for 28 days - 23 months** (n = 533 drugs)			**Drugs prescribed for 2 - 11 years** (n = 1302 drugs)			**Drugs prescribed for 12 - 18 years** (n = 725 drugs)		
Drugs	**Freq**	**%**	**Drugs**	**Freq**	**%**	**Drugs**	**Freq**	**%**	**Drugs**	**Freq**	**%**
Cephazolin	1	1.1	Dilacaine	11	2.1	Dexamethasone	11	0.8	Cisretinoic acid	1	0.1
			Dexamethasone	9	1.7	Adrenaline	3	0.2	Gonadorelin	1	0.1
			Adrenaline	4	0.8	Carnitine	2	0.1	Salicylic acid/ cetylpyridinium	1	0.1
			Sodium chloride	3	0.6	Picibanil	1	0.1	Sodium chloride	1	0.1
			Aspirin	2	0.4	Azathioprine	1	0.1	Tocilizumab	1	0.1
			Domperidone	2	0.4	Dilacaine	1	0.1	Trichloracetic acid paste	1	0.1
			Azathioprine	1	0.2	Gonadorelin	1	0.1			
			Carnitine	1	0.2	Magnesium chloride	1	0.1			
			Propranolol	1	0.2	Metolazone	1	0.1			
			Tinidazole	1	0.2	Tacrolimus	1	0.1			

In summary, the rates identified in the study of prescribing off-label and unlicensed medicines are as shown in Table 3.41.

Table 3.41- Overall rates of off-label and unlicensed prescribing

Classification	Rate per 1000	
	Off-label	**Unlicensed**
Patients admitted	331	34
Patients admitted and prescribed drugs	491	50
Patients admitted as inpatients and prescribed drugs	781	33
Patients classified as outpatients and prescribed drugs	266	63
Patients admitted as emergency cases and prescribed drugs	396	56

Chapter 4

Lincomycin Results

4.1 Analytical methods

4.1.1 Assay for lincomycin hydrochloride HPLC optimisation

Results for the retention times of HPLC analysis of Lincocin® (which contains lincomycin hydrochloride and benzyl alcohol) using either a Prosphere® or Apollo® C18 columns with different ratios of acetonitrile and water in the mobile phase, as indicated in Section 2.11.1, are summarised in Table 4.1.

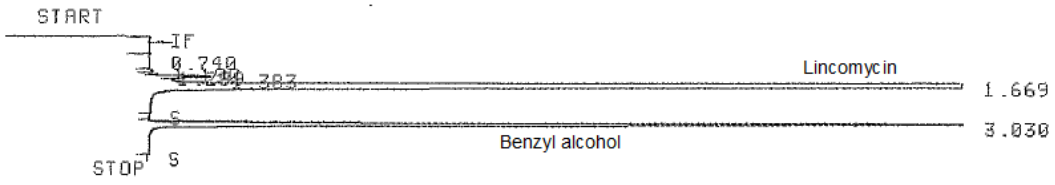
Separation of lincomycin hydrochloride and benzyl alcohol peaks was achieved with the Prosphere® column using a mobile phase containing either 8%, 10% and 15% acetonitrile, a flow rate of 1.5 mL/min and wavelength of 220nm (Figure 4.1). At each of these concentrations of acetonitrile, lincomycin hydrochloride was eluted before benzyl alcohol.

A mobile phase containing 5 % acetonitrile did not produce acceptable peak separation and peaks were of poor shape. There was also a reversal of lincomycin hydrochloride and benzyl alcohol elution times where benzyl alcohol eluted before lincomycin (Figure 4.2).

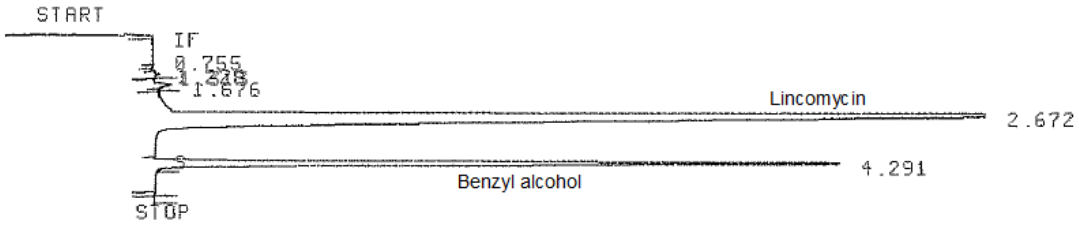
Superior separation of peaks was obtained using the C18 reverse phase Apollo® column. The results showed that 40% acetonitrile and 60% water containing 50 mM phosphoric acid at a flow rate of 1.5 mL/min and wavelength of 220 nm produced good benzyl alcohol and lincomycin peaks but the peaks were too close together (Figure 4.3a). At these conditions benzyl alcohol, which was also injected as a separate solution (Figure 4.3b), gave a clear peak at 2.374 minutes, with baseline separation of benzyl alcohol from lincomycin.

Table 4.1 - Results for lincomycin hydrochloride and benzyl alcohol HPLC analyses to determine optimum conditions using Prosphere® and Apollo® C18 columns and different ratios of acetonitrile and water in the mobile phase

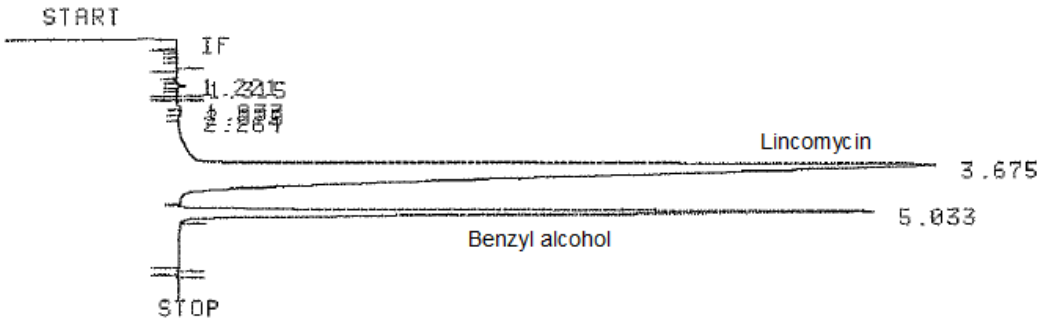
Column	**Acetonitrile** (%)	**Lincomycin hydrochloride retention time** (minutes)	**Benzyl alcohol retention time** (minutes)	**Result**
Prosphere®	15	1.7	3	Both peak shapes acceptable
Prosphere®	10	2.7	4.3	Both peak shapes acceptable
Prosphere®	8	3.7	5	Both peak shapes acceptable
Prosphere®	5	7.6	7	Lincomycin showed poor peak shape; benzyl alcohol showed acceptable peak shape.
Apollo®	40	~ 1.0	2.4	Both peak shapes acceptable
Apollo®	25	1.5	4	Both peak shapes acceptable
Apollo®	15	2.5	7.8	Both peak shapes acceptable
Apollo®	12	3.8	10.7	Both peak shapes acceptable
Apollo®	5	>20	>20	Lincomycin showed poor peak shape; benzyl alcohol showed poor peak shape.



(a) 15% acetonitrile and 85% water.



(b) 10% acetonitrile and 90% water.



(c) 8% acetonitrile and 92% water.

Figure 4-1 - HPLC traces showing the separation of lincomycin hydrochloride and benzyl alcohol using a Prosphere® column and different concentrations of acetonitrile and water in the mobile phase. Concentrations of (a) 15%, (b) 10% and (c) 8% acetonitrile are shown. A flow rate of 1.5 mL/min and wavelength of 220 nm were used.

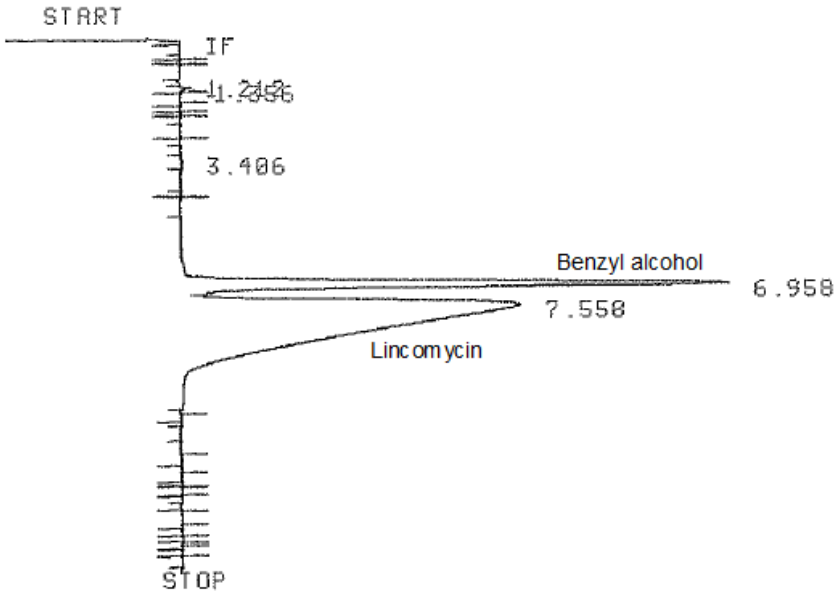
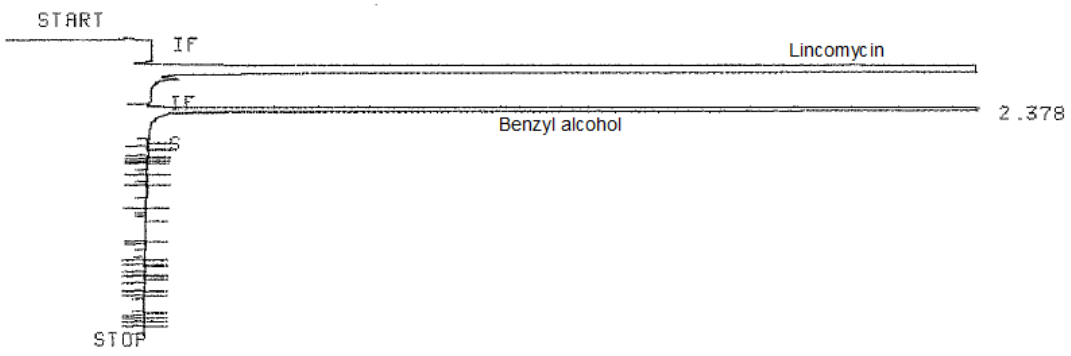
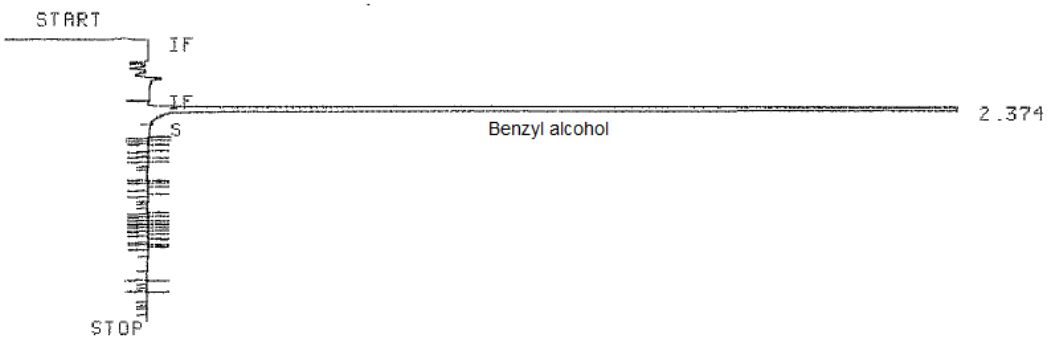


Figure 4-2 - Separation of lincomycin hydrochloride and benzyl alcohol peaks using a Prosphere® column and mobile phase of 5% acetonitrile and 95% water. The flow rate was 1.5 mL/min and wavelength 220 nm.



(a) Separation of lincomycin and benzyl alcohol peaks.



(b) Benzyl alcohol elution at 2.374 minute.

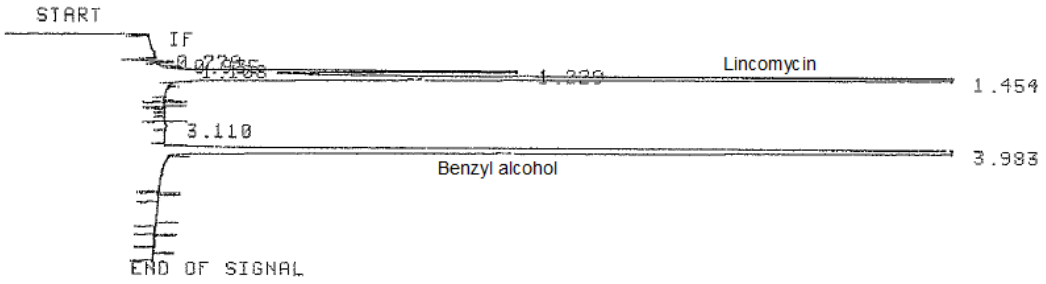
Figure 4-3 - Diagram (a) shows separation of lincomycin hydrochloride and benzyl alcohol peaks using a 1 in 100 dilution of Lincocin® and a C_{18} reverse phase Apollo® column, with a mobile phase of 40% acetonitrile and 60% water containing 50 mM phosphoric acid at a flow rate of 1.5 mL/min and wavelength of 220 nm; (b) shows pure benzyl alcohol.

Changing the mobile phase to 25% acetonitrile and 75% water containing 50 mM phosphoric acid at pH 3 (flow rate 1.5 mL/min, wavelength 220 nm) produced two peaks that were separated satisfactorily however, lincomycin hydrochloride was eluted at the solvent front, which was not satisfactory (Figure 4.4a). Using the same mobile phase but a wavelength of 260 nm, a peak for benzyl alcohol only was produced (without lincomycin hydrochloride) thereby confirming the maximum absorption of benzyl alcohol at this wavelength (Figure 4.4b).

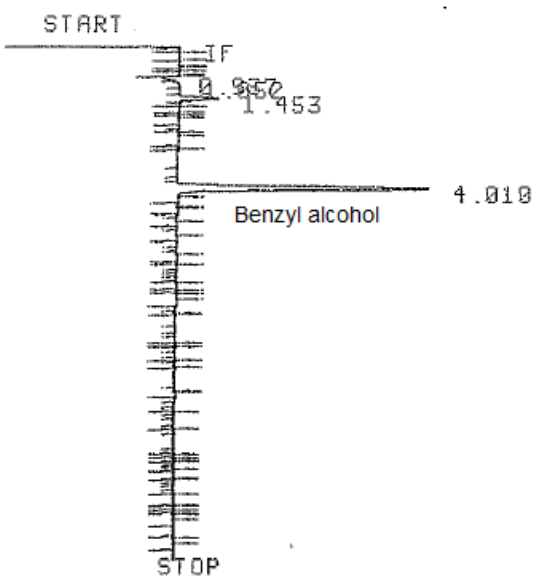
A mobile phase consisting of 15% acetonitrile and 85% water containing 50 mM phosphoric acid at pH 3 and wavelength of 220 nm produced two good peaks separating lincomycin hydrochloride and benzyl alcohol (Figure 4.5). An attenuation of 6, which had been used for all previous traces, was maintained but the peaks produced were too large. Hence the attenuation was changed to 10 which produced peaks on a suitable scale. However as can be seen in Figure 4.5, the lincomycin hydrochloride peak was still close to the solvent front.

Using a mobile phase consisting of 5% acetonitrile and 95% water containing 50 mM phosphoric acid at pH 3 did not produce a good result as the peaks were too close together and too distant from the solvent front.

A mobile phase of 12% acetonitrile and 88% water containing 50 mM phosphoric acid at pH 3 produced the optimum conditions on the C_{18} reverse phase Apollo® column (Figure 4.6). This was used for further analysis including stability of lincomycin hydrochloride at 60°C in acid (HCl), base (NaOH) and hydrogen peroxide.



(a) Separation of lincomycin and benzyl alcohol.



(b) Benzyl alcohol elution at 4.018 minutes.

Figure 4-4 - Diagram (a) shows lincomycin hydrochloride and benzyl alcohol peaks using a 1 in 100 dilution of Lincocin® and a C_{18} reverse phase Apollo® column, with a mobile phase of 25% acetonitrile and 75% water containing 50 mM phosphoric acid at a flow rate of 1.5 mL/min and wavelength of 220 nm; (b) shows pure benzyl alcohol at a wavelength of 260 nm.

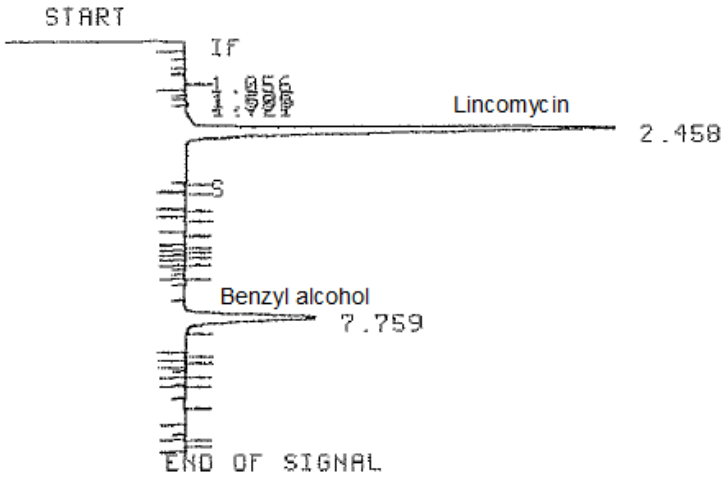


Figure 4-5 - Separation of lincomycin hydrochloride and benzyl alcohol peaks using a C_{18} reverse phase Apollo® column, with a mobile phase of 15% acetonitrile and 85% water containing 50 mM phosphoric acid at a flow rate of 1.5 mL/min and wavelength of 220 nm.

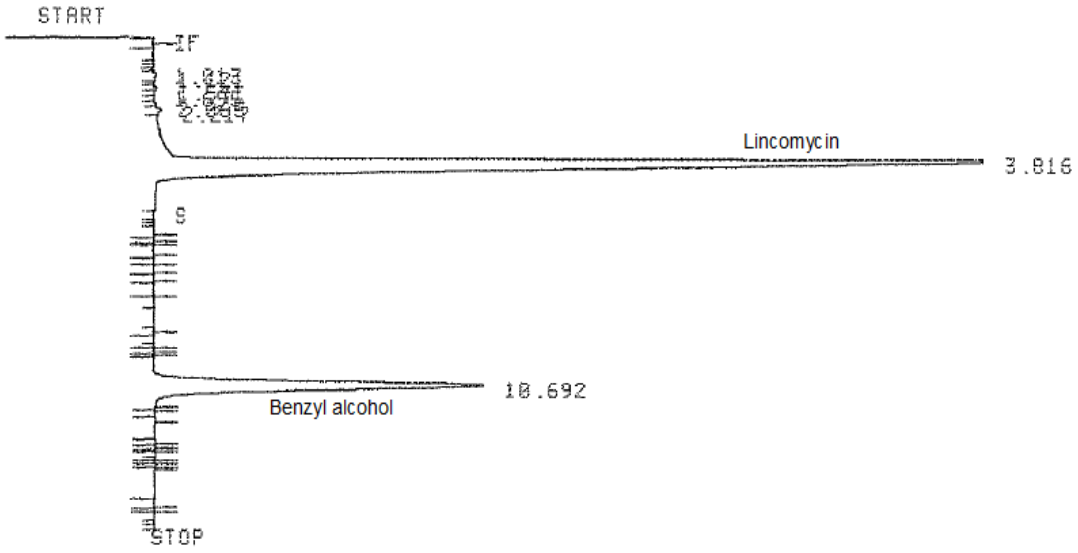


Figure 4-6 - Separation of lincomycin hydrochloride and benzyl alcohol peaks using a C_{18} reverse phase Apollo® column, with a mobile phase of 12% acetonitrile and 88% water containing 50 mM phosphoric acid at a flow rate of 1.5 mL/min and wavelength of 220 nm.

4.1.2 Assay validation

4.1.2.1 Calibration curve of Lincocin®

The linearity of the detector response for a range of Lincocin® (lincomycin hydrochloride) concentrations was determined to validate the reverse phase HPLC method. The assay was found to produce a linear relationship between the peak area and concentrations of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8 and 1.0 mg/mL lincomcyin hydrochloride with a regression coefficient (R^2) of 0.9993 as shown in Figure 4.7.

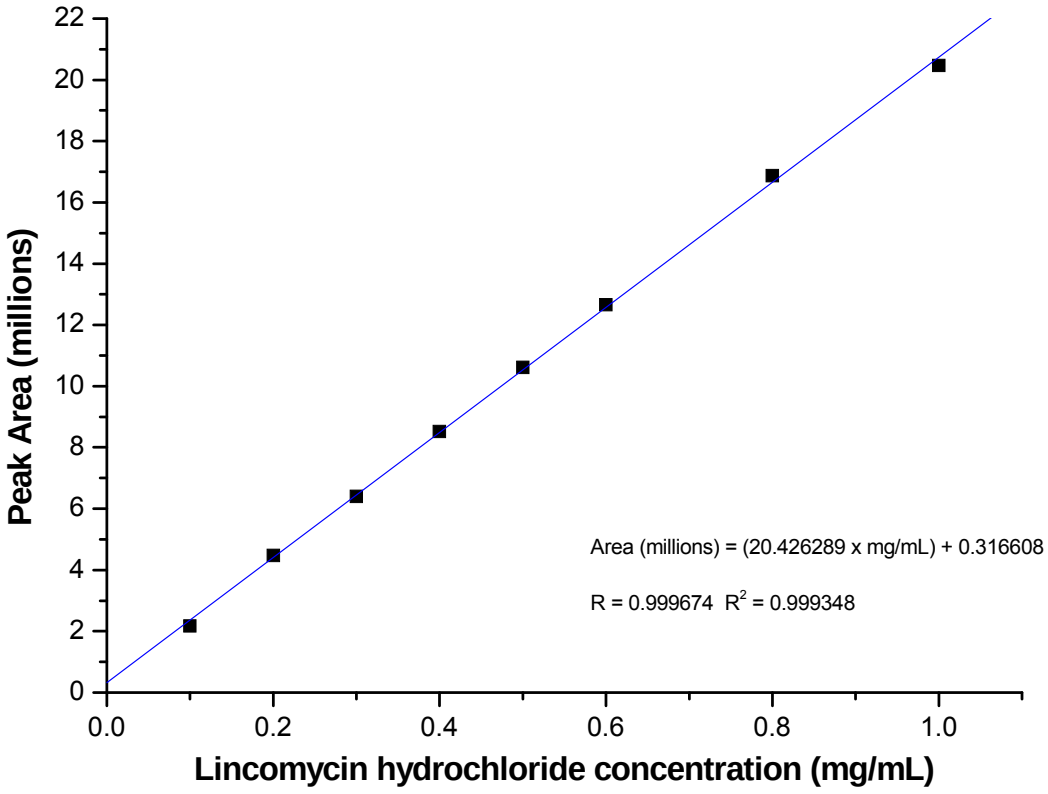


Figure 4-7 - Lincomycin hydrochloride calibration curve using solutions of Lincocin®.

4.1.2.2 Calibration curve of pure analytical grade lincomycin

The linearity of the detector response for a range of pure analytical grade lincomycin hydrochloride monohydrate concentrations was determined to validate the reverse phase HPLC method and to determine the amount of lincomycin in a freshly prepared 0.6 mg/mL lincomycin hydrochloride sample using Lincocin® injection. The assay was found to produce a linear relationship between the peak area and concentrations of lincomcyin hydrochloride monohydrate with a regression coefficient (R^2) of 0.9999 as shown in Figure 4.8.

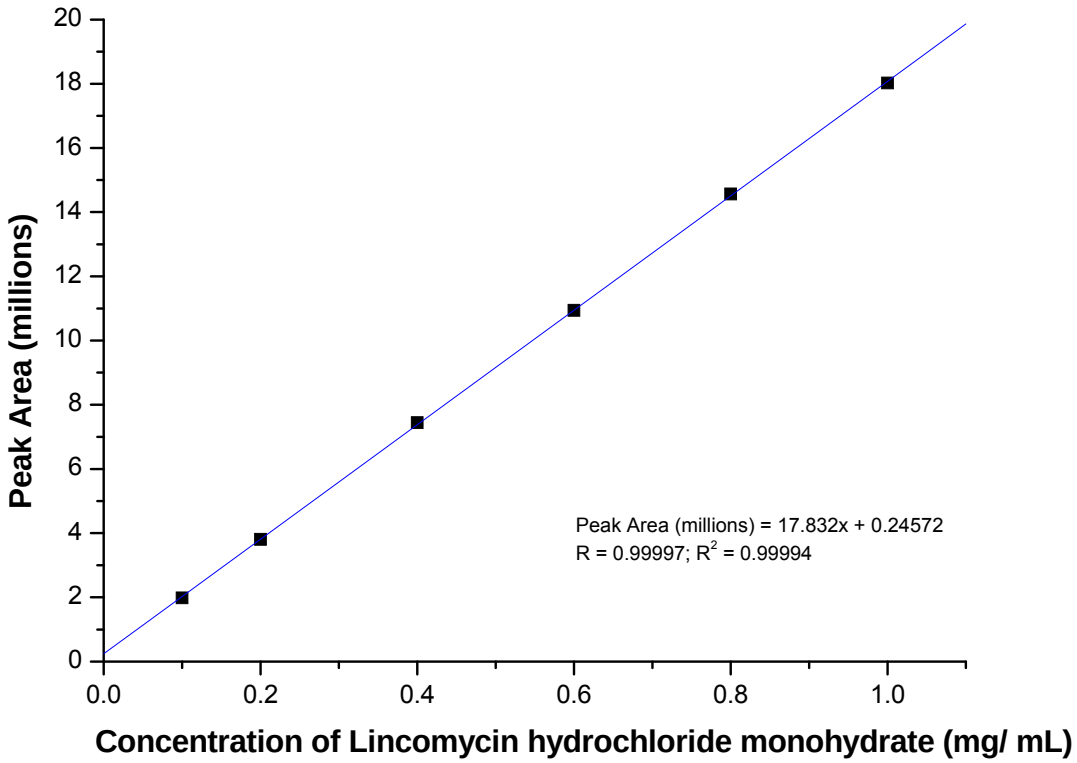


Figure 4-8 - Calibration curve prepared from analytical grade lincomycin hydrochloride monohydrate standard.

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The above calibration curve was used to determine the amount of lincomycin base in the 0.6 mg/mL lincomycin hydrochloride sample prepared from Lincocin® and was found to contain 0.629 mg/mL lincomycin. This was equivalent to 104.9% of the stated amount. According to the British Pharmacopeia (BP) 2013,[36] the specifications for the content of lincomycin in lincomycin injection is 92.5 to 107.5% of the stated amount. The calculated quantity of lincomycin in Lincocin® injections (104.9%) meets the specifications of the BP.

4.1.2.3 Inter- and intra-day variability

Table 4.2 shows the results obtained when six separate injections of 0.6 mg/mL lincomycin hydrochloride (Lincocin®) were analysed consecutively on two separate days. The minimum and maximum HPLC results, mean, standard deviation, variance and coefficient of variation percentage are shown in Table 4.3. The coefficient of variation for both day one and two was identical at 0.63%.

Table 4.2 - HPLC results obtained on two separate days after six individual injections of a standard 0.6 mg/mL lincomycin hydrochloride (Lincocin®) solution

Sample	Day 1 (Peak area)	Day 2 (Peak area)
1	13186480	12823912
2	13408640	12926984
3	13183768	13053792
4	13235680	12852992
5	13259464	12928080
6	13292888	12813832

Table 4.3 - The minimum and maximum HPLC values, mean, standard deviation, variance and coefficient of variation percentage of 0.6 mg/mL lincomycin hydrochloride tested on two days

Analysis	Day 1	Day 2
Minimum (Peak area)	13183768	12813832
Maximum (Peak area)	13408640	13053792
Mean (Peak area)	13261153	12899932
Standard deviation	83637	90102
Variance	7.0×10^9	8.11×10^9
Coefficient of Variation (%)	0.63	0.63

4.1.3 Stability indicating HPLC method

To determine the stability indicating nature of the assay, lincomycin hydrochloride was subjected to forced degradation in acid and base solutions at 60°C.

4.1.3.1 Initial acid and alkali degradation

Results for the initial stability indicating test of 6 mg/mL lincomycin hydrochloride in 0.1 M HCl or 0.1 M NaOH solutions over 24 hours at 60°C are shown in Table 4.4 and Table 4.5. The results indicated that lincomycin hydrochloride underwent a slow degradation process but degradation occurred more rapidly in base solutions than acid solutions. This is evidenced by a lower area under the curve value at 24 hours in sodium hydroxide solution.

Table 4.4 - HPLC area under the curve results of 6 mg/mL lincomycin hydrochloride indicating its degradation over a 24 hour period in 0.1 M HCl solution at 60°C

Time of sampling (hours)	**Peak Area under curve**		**Peak height**	
		(%)	(mm)	(%)
0.0	48670592	100.0	137.0	100.0
2.0	-		-	
4.0	54803360	112.6	141.5	103.3
6.0	52338144	107.5	139.5	101.8
7.0	52366976	107.6	138.5	101.1
24.0	48792640	100.3	131.0	95.6

Table 4.5 - HPLC area under the curve results of 6 mg/mL lincomycin hydrochloride indicating its degradation over a 24 hour period in 0.1 M NaOH solution at 60°C

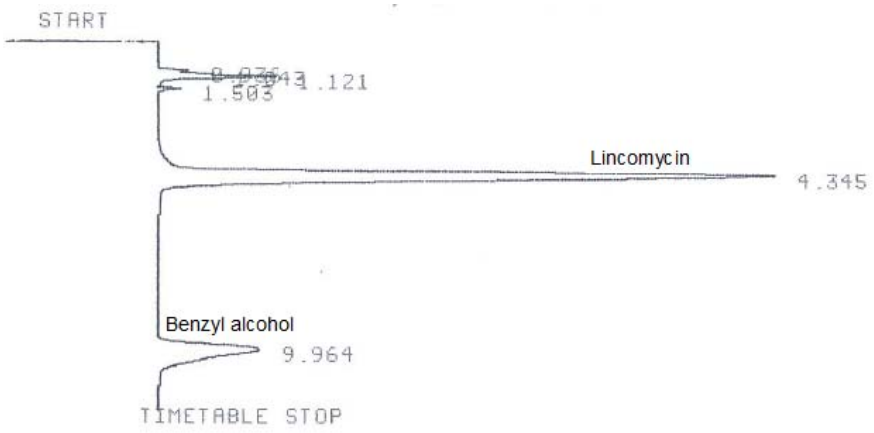
Time of sampling (hours)	**Peak Area under curve**		**Peak height**	
		(%)	(mm)	(%)
0.0	50392320	100.0	134.0	100.0
2.0	49080448	97.4	136.0	101.5
4.0	48243392	95.7	134.0	100.0
6.0	47010624	93.3	131.0	97.8
7.0	-		-	
24.0	39324096	78.0	115.0	85.8

4.1.3.2 Further stability testing in acid and alkali

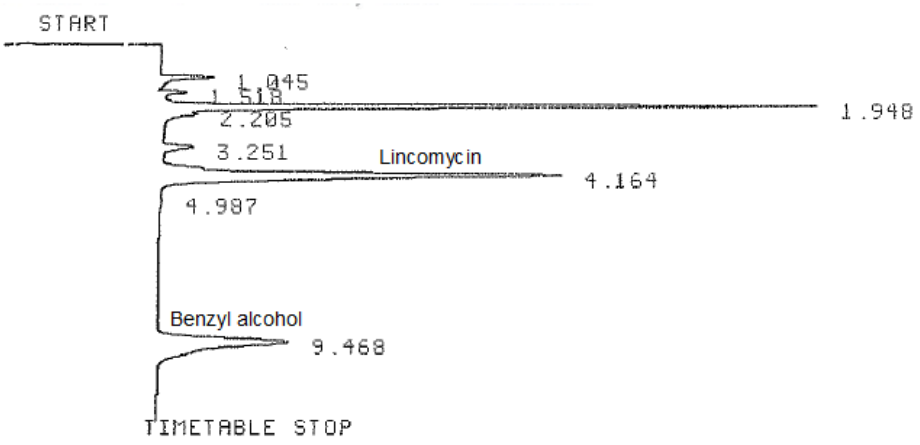
The results from seven day stability testing of 0.6 mg/mL lincomycin hydrochloride in 0.1 M hydrochloric acid and 0.1 M sodium hydroxide solution at 60°C are shown in Table 4.6. As can be seen, lincomycin hydrochloride showed less rapid degradation in acid than in base solutions with 48.8% lincomycin remaining in the acid solution after 7 days compared to 8.0% remaining in base solution after the same time. Figure 4.9 shows the initial and final HPLC traces of lincomycin hydrochloride in 0.1 M HCl. Figure 4.10 shows the initial and final traces of lincomycin hydrochloride in 0.1 M NaOH.

Table 4.6 - HPLC results showing the degradation of lincomycin hydrochloride in 0.1 M HCl and 0.1 M NaOH solutions at 60°C over 7 days

Time of Sampling		**Lincomycin hydrochloride in 0.1 M HCl Area under curve**		**Lincomycin hydrochloride in 0.1 M NaOH Area under curve**	
(hours)	(days)	(Peak area)	(%)	(Peak area)	(%)
0.0	**0.0**	6532634	100.0	6418883	100.0
6.0	**0.3**	6537232	100.1	6083315	93.8
24.0	**1.0**	6728099	103.0	4918394	76.6
30.0	**1.3**	5817482	89.1	4196714	65.4
48.0	**2.0**	5612877	85.9	3224552	50.2
54.0	**2.3**	5508173	84.3	2939918	45.8
72.0	**3.0**	4953027	75.8	2253712	35.1
78.0	**3.3**	4167718	63.8	2043185	31.8
96.0	**4.0**	3631354	55.6	1485735	23.1
102.0	**4.3**	3650494	55.9	1411459	22.0
120.0	**5.0**	3475410	53.2	964804	15.0
126.0	**5.3**	3384413	51.8	910042	14.2
144.0	**6.0**	3179478	48.7	685628	10.7
168.0	**7.0**	3186080	48.8	512264	8.0

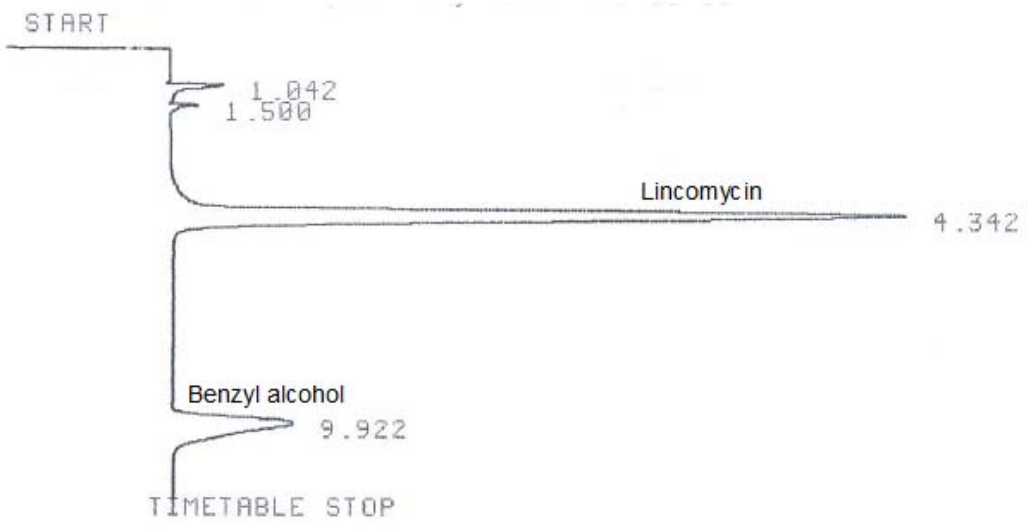


(a) Baseline peak of lincomycin hydrochloride in 0.1 M HCl solution

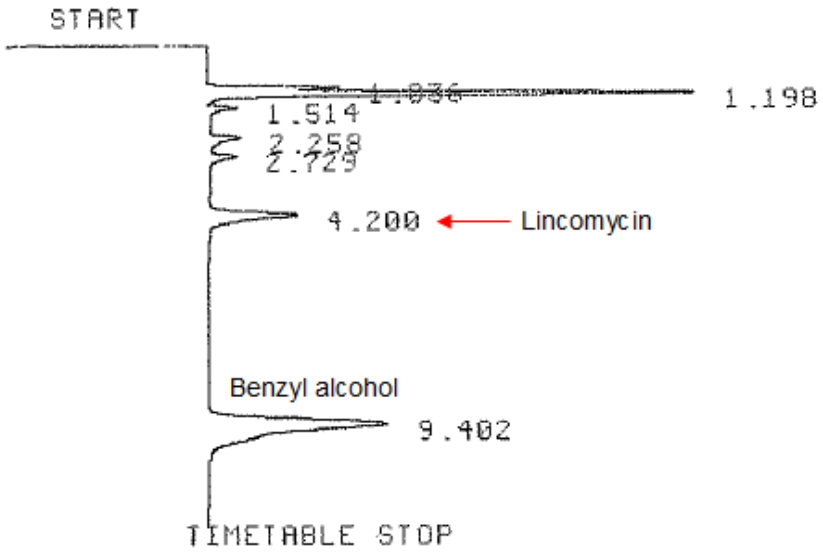


(b) Degradation of lincomycin hydrochloride in 0.1 M HCl solution after 7 days

Figure 4-9 - HPLC traces showing lincomycin peak at baseline (day zero) and after seven day treatment of 0.6 mg/mL lincomycin hydrochloride with 0.1 M HCl (a) and after seven days at 60°C (b). A flow rate of 1.5 mL/min was used and wavelength of 220 nm.



(a) Baseline peak of lincomycin hydrochloride in 0.1 M NaOH solution



(b) Degradation of lincomycin hydrochloride in 0.1 M NaOH solution after 7 days

Figure 4-10 -HPLC traces showing lincomycin peak at baseline (day zero) after treatment of 0.6 mg/mL lincomycin hydrochloride with 0.1 M NaOH (a) and after seven days at 60°C (b). A flow rate of 1.5 mL/min was used and wavelength of 220 nm

4.1.3.3 Hydrogen peroxide degradation

The results for the stability test of lincomycin hydrochloride in hydrogen peroxide at 60°C over 60 minutes are shown in Table 4.7. Lincomycin hydrochloride was shown to degrade most rapidly in 3% hydrogen peroxide compared to acid and base conditions. Figure 4.11 shows the exponential degradation of lincomycin hydrochloride in 3% hydrogen peroxide over 60 minutes. When the logarithm of peak area was plotted against time, the following linear relationship was produced:

$$\text{Log}_{10}\ \text{Peak Area} = -(0.03968 \times \text{hrs}) + 7.0225$$

with a correlation coefficient (R^2) of 0.98333 (Figure 4.11).

Table 4.7 - HPLC results for lincomycin hydrochloride in 3% hydrogen peroxide solutions at 60°C over 60 minutes

Time of Sampling (minutes)	**Peak Area of Lincomycin hydrochloride in Hydrogen peroxide** (Peak area)	(%)
0.0	7178880	100.0
5.0	5863210	81.7
10.0	4349565	60.6
15.0	2831058	39.4
20.0	1871485	26.1
25.0	1256313	17.5
30.0	801870	11.2
35.0	525966	7.3
40.0	343733	4.8
45.0	190615	2.7
50.0	114585	1.6
55.0	67297	0.9
60.0	25187	0.4

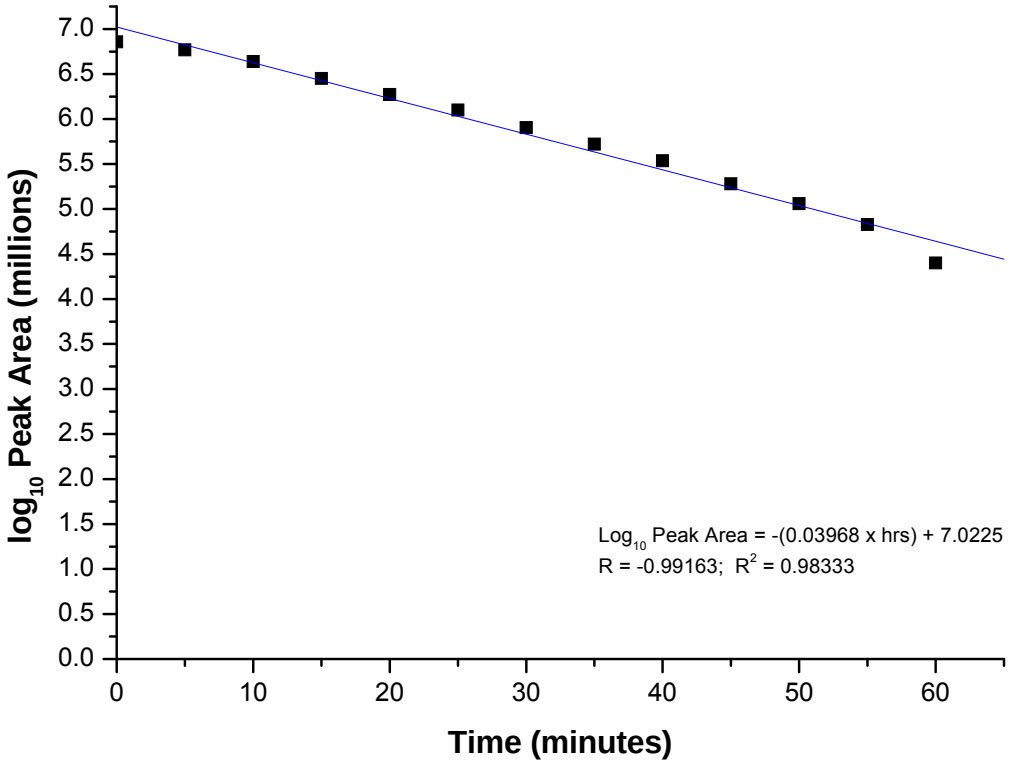
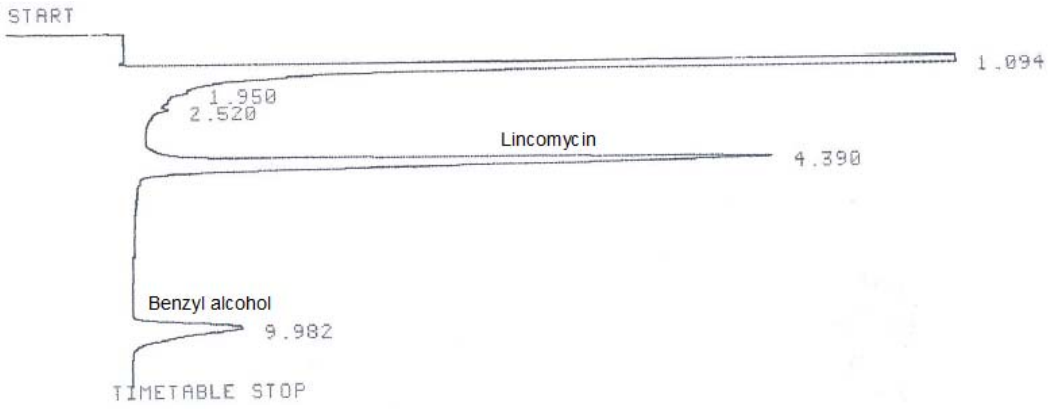


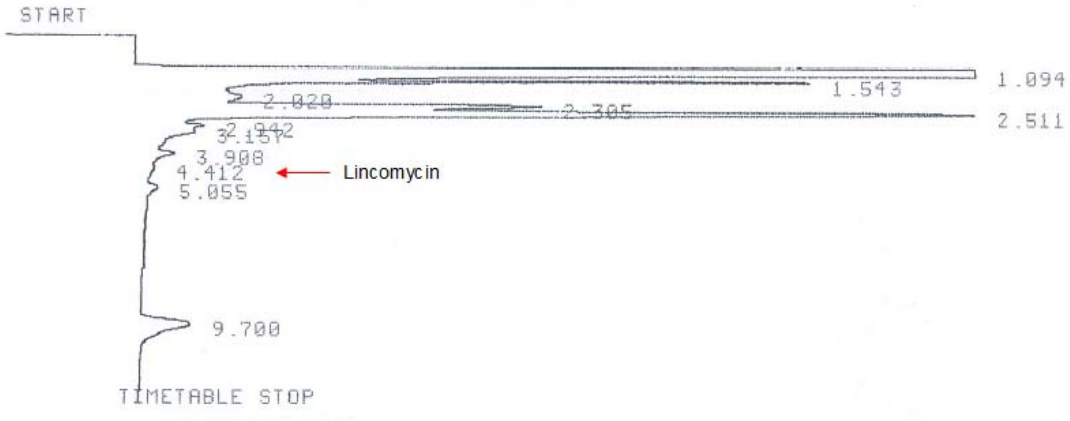
Figure 4-11 -Log peak area versus time for the degradation of 0.6 mg/mL lincomycin hydrochloride in 3% hydrogen peroxide

From Figure 4.11, the rate constant for the degradation of 0.6 mg/mL lincomycin hydrochloride in 3% hydrogen peroxide was calculated as 9.14 x 10^{-2} min^{-1} which corresponds to a shelf-life of 1.15 hours, suggesting that lincomycin hydrochloride readily undergoes oxidation.

HPLC traces showing the baseline chromatogram of lincomycin hydrochloride in 3% hydrogen peroxide and final HPLC tracing are shown in Figure 4.12. Only 0.4% lincomycin hydrochloride remained in the solution after 60 minutes.



(a) Baseline peak of lincomycin.

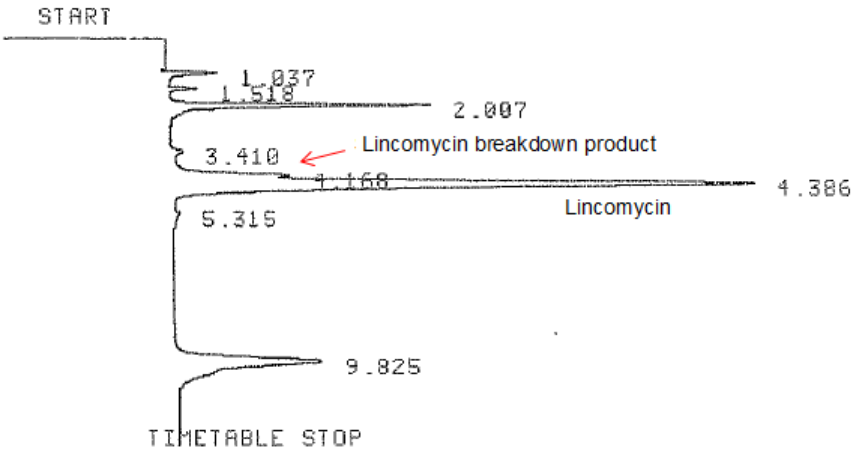


(b) Degradation of lincomycin after 60 minutes.

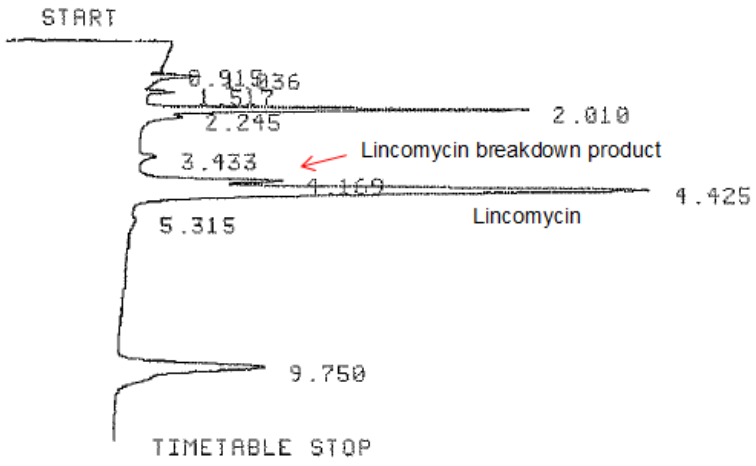
Figure 4-12 -HPLC traces showing lincomycin hydrochloride peak at baseline after treatment of 0.6 mg/mL lincomycin hydrochloride with 3% hydrogen peroxide (a) and after 60 minutes at 60°C (b). A flow rate of 1.5 mL/min was used and wavelength of 220 nm were used.

4.2 Optimisation for resolution of lincomycin breakdown products

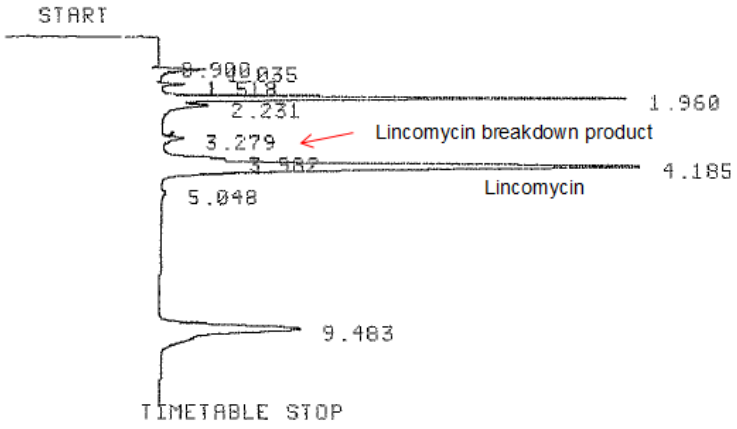
When 0.6 mg/mL lincomycin hydrochloride was prepared in 0.1 M HCl and stored at 60°C, evidence of the lincomycin hydrochloride breakdown product after 48 hours was seen in the HPLC trace (Figure 4.13.a). The breakdown product appeared as a lincomycin hydrochloride 'shoulder peak' at 4.168 minutes. After 72 hours (3 days) the breakdown product was much more evident (Figure 4.13b) and was eluted as a 'shoulder peak' at 4.169 minutes. After 96 hours (4 days), a small "shoulder peak" on lincomycin hydrochloride was seen at 3.987 minutes but was less evident (Figure 4.13c) and after 264 hours the "shoulder peak" was almost not visible.



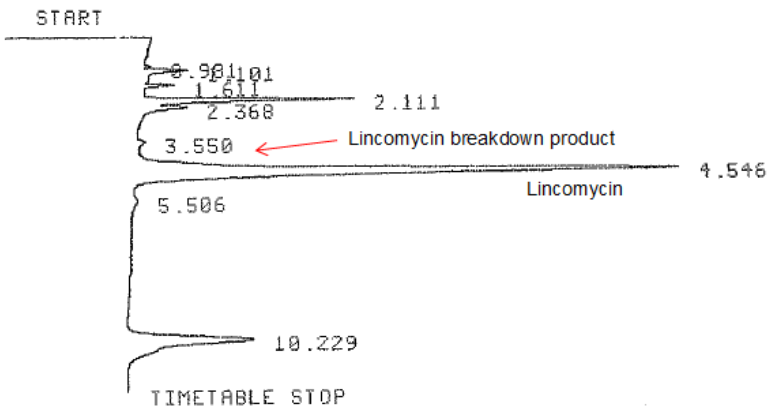
(a) Evidence of breakdown product after 48 hours.



(b) Evidence of breakdown product after 72 hours.



(c) Evidence of breakdown product after 96 hours (4 days).



(d) Evidence of breakdown product after 264 hours (11 days).

Figure 4-13 -Evidence of lincomcyin hydrochloride breakdown products after 48 hours (a), 72 hours (b), 96 hours (c) and 264 hours (d).

After 18 days, a sharp "shoulder peak" was again visible as part of the lincomycin hydrochloride peak at 4.150 minutes (Figure 4.14). To optimise the separation of lincomycin hydrochloride and the lincomycin hydrochloride breakdown product, a mobile phase consisting of 10% acetonitrile and 90% water was employed (Figure 4.15). This produced clear separation of peaks. The early sharp peak was eluted at 2.423 minutes, the "shoulder peak" at 4.301 minutes, lincomycin hydrochloride at 6.384 minutes and benzyl alcohol at 11.677 minutes. However, superior separation of peaks was achieved using an unused Apollo C18 column and a mobile phase consisting of 8% acetonitrile and 92% water (Figure 4.16) and all subsequent HPLC analysis was carried out using these concentrations. Decreasing the flow rate to 1.0 mL/min did not optimise results.

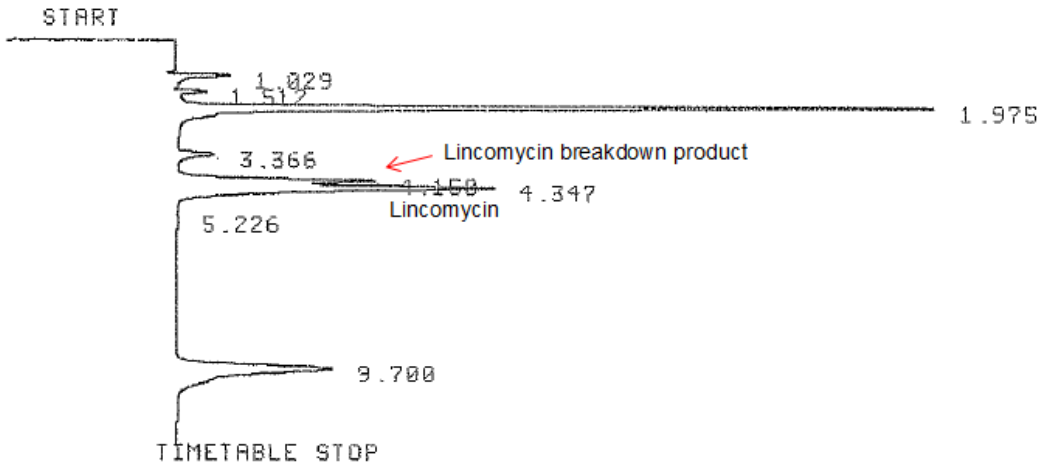


Figure 4-14 -Evidence of a lincomycin hydrochloride breakdown product after 18 days.

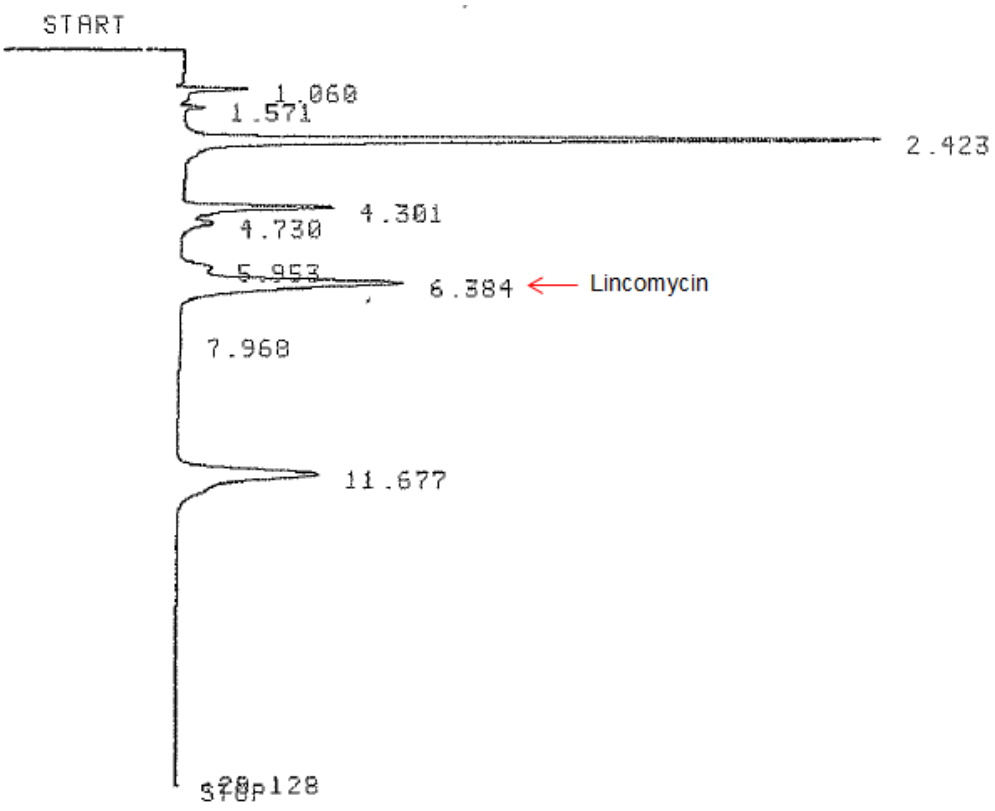


Figure 4-15 -Separation of lincomycin hydrochloride and lincomycin hydrochloride breakdown product peaks using a mobile phase of 10% acetonitrile and 90% water.

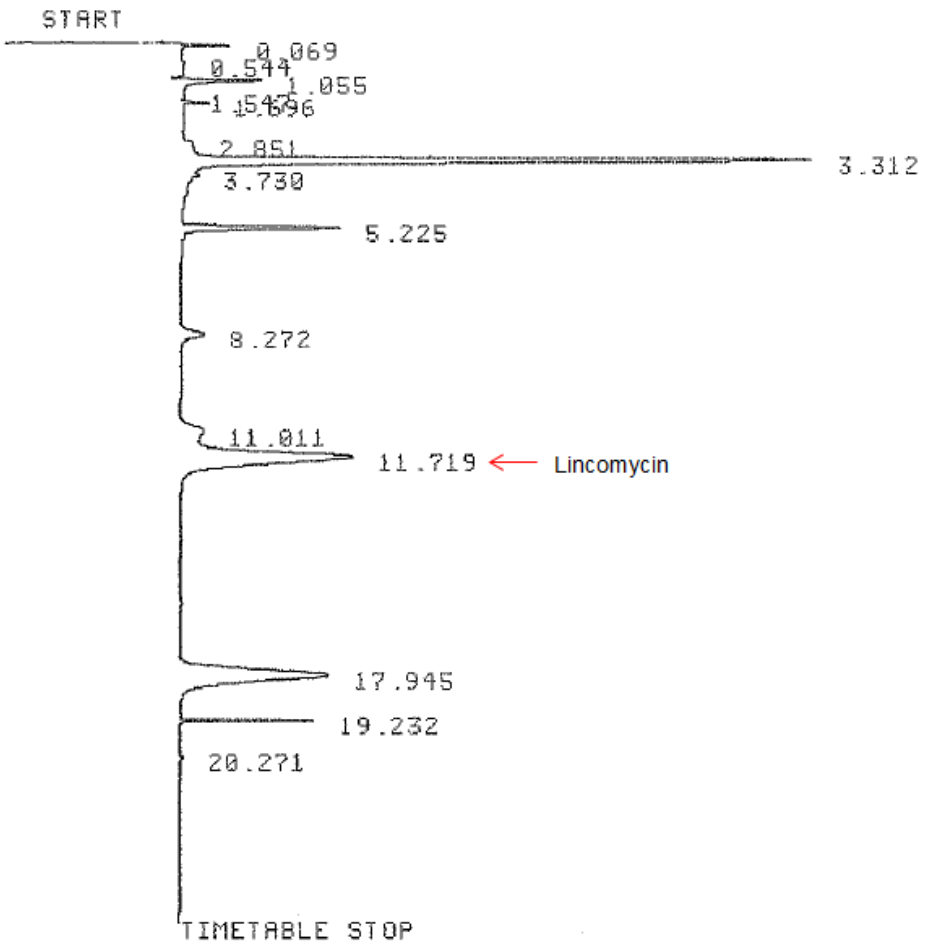


Figure 4-16 -Separation of lincomycin hydrochloride and lincomycin hydrochloride breakdown product peaks using a new Apollo® column and mobile phase of 8% acetonitrile and 92% water.

4.3 Stability indicating tests in IV fluids

4.3.1 Stability indicating test of 0.6 mg/mL lincomycin hydrochloride in 0.9% NaCl and sodium lactate (Hartmann's) solution

The pH of 0.6 mg/mL lincomycin hydrochloride in 0.9% NaCl solution and sodium lactate solution was determined over a period of 7 days at 60°C. The pH of sodium lactate (Hartmann's) solution and 0.9% NaCl solution was 5.9 and 5.79 respectively prior to the addition of lincomycin hydrochloride. A slight change in pH was observed at time zero after the addition of 0.6 mg/mL lincomycin hydrochloride to each IV solution. However, Table 4.8 shows that lincomycin hydrochloride in 0.9% sodium chloride and sodium lactate (Hartmann's) solution was very stable and there was no measurable change in concentration for a period of time. We can conclude that the shelf-life of lincomycin hydrochloride in 0.9% sodium chloride or sodium lactate (Hartmann's) solution at 60°C is at least 7 days.

Table 4.8 - pH obtained for lincomycin hydrochloride in sodium lactate and 0.9% sodium chloride solution over 7 days at 60°C

Sampling Time (hours)	pH of 0.6 mg/mL lincomycin hydrochloride in sodium lactate (Hartmann's) solution	pH of 0.6 mg/mL lincomycin hydrochloride in 0.9% NaCl solution
0.0	5.81	5.70
2.0	5.86	6.07
4.0	5.91	6.03
24.0	6.01	6.01
26.0	5.91	5.99
48.0	5.99	6.03
50.0	6.01	6.10
54.0	6.03	6.16
72.3	6.03	6.13
76.0	6.01	6.07
100.0	6.04	6.18
143.0	6.07	6.28
145.0	6.08	6.30
168.0	6.07	6.35

4.3.2 Stability testing of 0.6 mg/mL lincomycin hydrochloride at room temperature (25°C)

The stability of lincomycin hydrochloride was tested in IV solutions including sodium lactate (Hartmann's) solution, 0.9% sodium chloride solution, 5% glucose solution and 10% glucose solution.

Lincomycin hydrochloride was found to be stable in sodium lactate (Hartmann's) solution with only a small proportion degrading over the 31 day period at 25°C (Table 4.9).

Lincomycin hydrochloride was found to be more stable in 0.9% sodium chloride solution than in sodium lactate (Hartmann's) solution, with less than 2% lincomycin hydrochloride degrading over the 31 day period at 25°C (Table 4.10).

Lincomycin hydrochloride was found to be more stable in 5% glucose solution than in sodium lactate (Hartmann's) solution, but less stable than in 0.9% NaCl solution with less than 5% lincomycin hydrochloride degrading over the 31 day period at 25°C (Table 4.11).

Lincomycin hydrochloride showed similar stability in 10% glucose compared to 5% glucose solution. It was more stable than in sodium lactate (Hartmann's) solution, but less stable than in 0.9% NaCl solution with less than 5% lincomycin degrading over the 31 day period at 25°C (Table 4.12).

As can be seen from the results in Tables 4.9 to 4.12, lincomycin hydrochloride was very stable in sodium lactate (Hartmann’s) solution, 0.9% sodium chloride solution, 5% glucose solution and 10% glucose solutions. All samples had a shelf-life of 744 hours or 31 days.

Table 4.9 - Results for the degradation of 0.6 mg/mL lincomycin hydrochloride at 25°C in sodium lactate (Hartmann's) solution over 31 days

Time (hours)	**pH**	**Sodium lactate Peak Area**	**Log_{10} Peak Area**	**Percentage of baseline AUC**	**Log_{10} Percentage of baseline AUC**
0.0	6.28	6297749	6.7992	100.0	2.0000
24.0	6.26	6141936	6.7883	97.5	1.9890
96.0	6.22	6298190	6.7992	100.0	2.0000
168.0	6.23	6271727	6.7974	99.6	1.9983
264.0	6.30	6307764	6.7999	100.2	2.0009
336.0	6.27	6409389	6.8068	101.8	2.0078
409.7	6.35	6189187	6.7916	98.3	1.9926
575.5	6.34	6168075	6.7901	97.9	1.9908
744.0	6.44	6266224	6.7970	99.5	1.9978

Table 4.10 - Results for the degradation of 0.6 mg/mL lincomycin hydrochloride at 25°C in 0.9% sodium chloride solution over 31 days

Time (hours)	**pH**	**0.9% NaCl Peak Area**	**Log_{10} Peak Area**	**Percentage of baseline AUC**	**Log_{10} Percentage of baseline AUC**
0.0	5.87	6426908	6.8080	100.0	2.0000
24.0	5.75	6193777	6.7920	96.4	1.9841
96.0	5.80	6384620	6.8051	99.3	1.9970
168.0	5.87	6341349	6.8022	98.7	1.9943
264.0	5.97	6429204	6.8082	100.0	2.0000
336.0	5.75	6442411	6.8090	100.2	2.0009
410.8	5.68	6419509	6.8075	99.9	1.9996
575.5	5.80	6345487	6.8025	98.7	1.9943
744.0	5.79	6263480	6.7968	97.5	1.9890

Table 4.11 - Results for the degradation of 0.6 mg/mL lincomycin hydrochloride at 25°C in 5% glucose solution over 31 days

Time (hours)	**pH**	**5% Glucose Peak Area**	**Log_{10} Peak Area**	**Percentage of baseline AUC**	**Log_{10} Percentage of baseline AUC**
0.0	3.49	6569197	6.8175	100.0	2.0000
24.0	3.51	6245656	6.7956	95.1	1.9782
96.0	3.52	6435503	6.8086	98.0	1.9912
168.0	3.60	6366680	6.8039	96.9	1.9863
264.0	3.53	6474652	6.8112	98.6	1.9939
336.0	3.50	6250465	6.7959	95.1	1.9782
410.8	3.47	6565427	6.8173	99.9	1.9996
575.5	3.37	6424328	6.8078	97.8	1.9903
744.0	3.45	6458256	6.8101	98.3	1.9926

Table 4.12 - Results for the degradation of 0.6 mg/mL lincomycin hydrochloride at 25°C in 10% glucose solution over 31 days

Time (hours)	**pH**	**10% Glucose Peak Area**	**Log 10 Peak Area**	**Percentage of baseline AUC**	**Log10 Percentage of baseline AUC**
0.0	3.73	6427563	6.8080	100.0	2.0000
24.0	3.67	6345394	6.8025	98.7	1.9943
96.0	3.73	6429390	6.8082	100.0	2.0000
168.0	3.65	6364180	6.8037	99.0	1.9956
264.0	3.61	6462238	6.8104	100.5	2.0022
336.0	3.62	6312479	6.8002	98.2	1.9921
410.8	3.63	6526265	6.8147	101.5	2.0065
575.7	3.55	6281076	6.7980	97.7	1.9899
744.0	3.52	6395738	6.8059	99.5	1.9978

4.4 Lincomycin stability studies

4.4.1 Stability studies of lincomycin in acid at 60°C over 12 days to determine the rate constant

The stability of a 0.6 mg/mL stock solution of lincomycin hydrochloride in 0.1 M HCl at 60°C was evaluated by HPLC analysis using a mobile phase consisting of 8% acetonitrile and 92% water. The degradation of lincomycin hydrochloride follows first order kinetics as is shown in Figure 4.17.

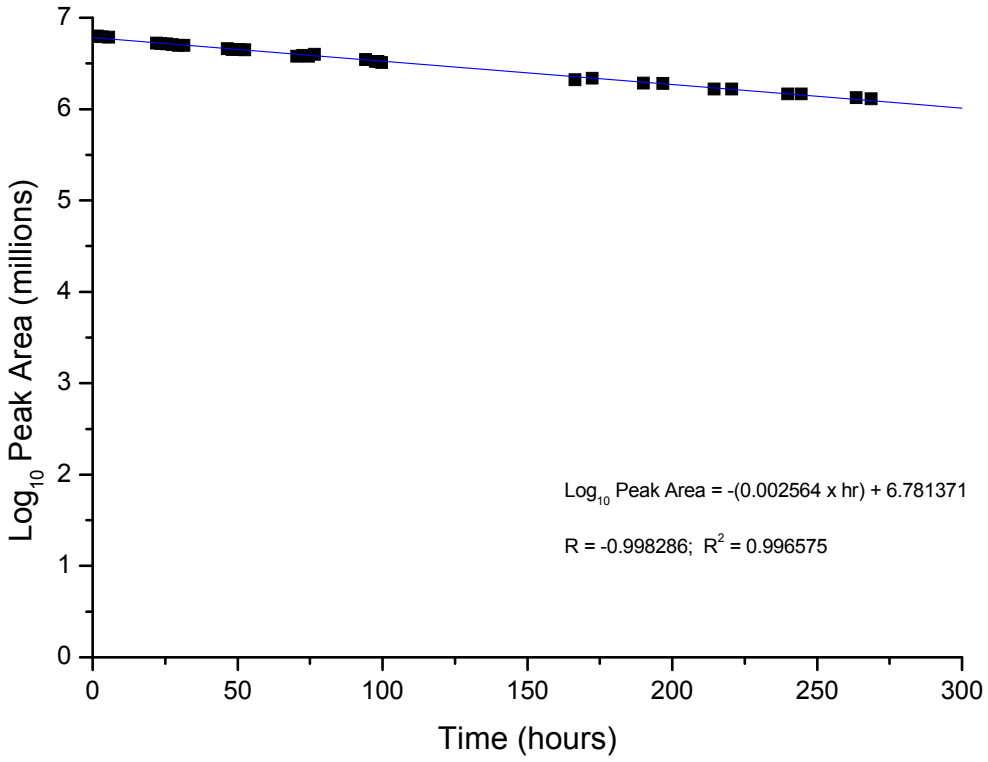


Figure 4-17–Degradation of lincomycin hydrochloride in 0.1 M HCl at 60°C over 12 days.

The equation of the degradation curve in Figure 4.17 was used to calculate a rate constant of $5.90 \pm 0.03.x\ 10^{-3}\ hr^{-1}$.

4.4.2 Lincomycin stability in buffer solutions

Table 4.13 shows the HPLC data of 0.6 mg/mL lincomycin hydrochloride obtained at pH 2.00. The degradation of lincomycin hydrochloride at pH 2.00 is shown graphically in Figure 4.18, which shows $\log_{10}$ area versus time and $\log_{10}$ percent of lincomycin hydrochloride.

Table 4.13 - HPLC data on the degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 2.00

Time (hours)	**pH**	**Peak Area of lincomycin hydrochloride at pH 2.00**	**$\log_{10}$ Peak Area**	**Percentage of baseline AUC**	**$\log_{10}$ Percentage of baseline AUC**
0.0	1.99	6811984	6.8333	100.0	2.0000
19.0	2.01	4884208	6.6888	71.7	1.8555
23.0	1.88	4927843	6.6927	72.3	1.8591
43.0	1.88	3642618	6.5614	53.5	1.7284
48.5	1.88	3375061	6.5283	49.5	1.6946
67.0	2.01	2769046	6.4423	40.6	1.6085
91.0	1.96	2106157	6.3235	30.9	1.4900
139.0	1.92	1242386	6.0943	18.2	1.2601
163.0	1.98	950851	5.9781	14.0	1.1461
187.0	1.91	738960	5.8686	10.8	1.0334
211.0	1.95	570899	5.7566	8.4	0.9243
235.0	1.95	437606	5.6411	6.4	0.8062
259.0	1.95	324447	5.5111	4.8	0.6812

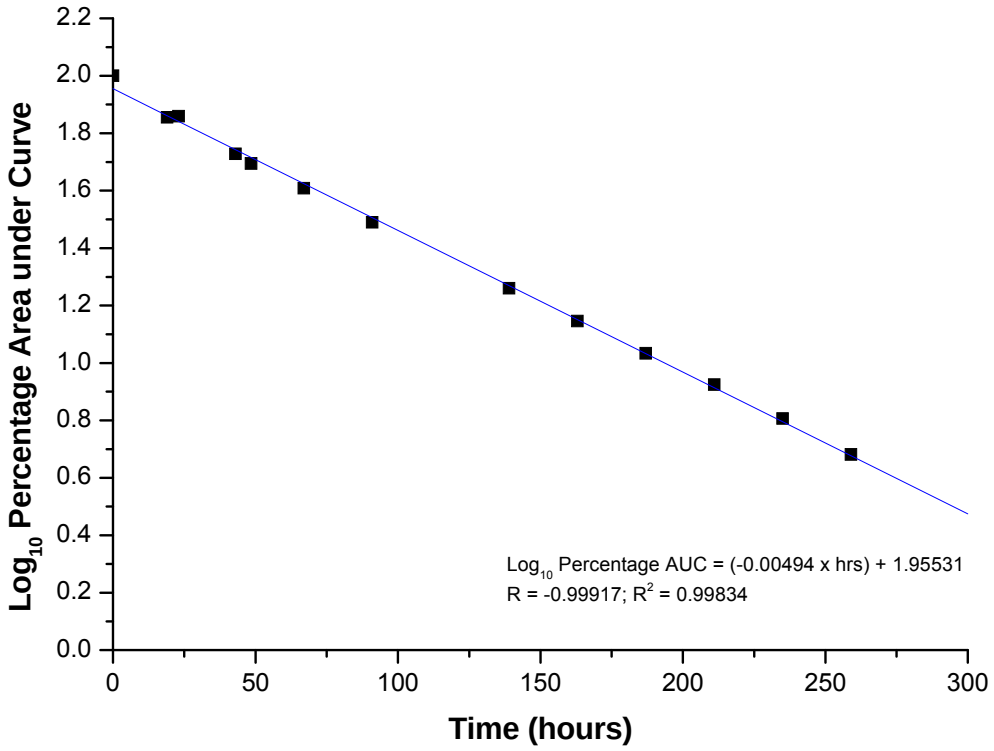


Figure 4-18 -Degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 2.00 (I = 0.5).

Table 4.14 shows the HPLC data of 0.6 mg/mL lincomycin hydrochloride obtained at pH 3.10. The degradation of lincomycin hydrochloride at pH 3.10 is shown graphically in Figure 4.19, which shows $\log_{10}$ area versus time and $\log_{10}$ percent of lincomycin hydrochloride.

Table 4.15 shows the HPLC data of 0.6 mg/mL lincomycin hydrochloride obtained at pH 4.00. The degradation of lincomycin hydrochloride at pH 4.00 is shown graphically in Figure 4.20, which shows $\log_{10}$ area versus time and $\log_{10}$ percent of lincomycin hydrochloride.

Table 4.14 - HPLC data showing the degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 3.10

Time (hours)	pH	Peak Area of lincomycin hydrochloride at pH 3.10	Log_{10} Peak Area	Percentage of baseline AUC	Log_{10} Percentage of baseline AUC
0.0	3.11	6246531	6.7956	100.0	2.0000
24.0	3.11	6243854	6.7955	100.0	1.9998
47.8	3.08	6012065	6.7790	96.3	1.9834
122.5	3.04	5472902	6.7382	87.6	1.9426
141.0	3.08	5172219	6.7137	82.8	1.9180
167.0	3.11	4783645	6.6798	76.6	1.8841
192.0	3.10	4598690	6.6626	73.6	1.8670
211.5	3.10	4526065	6.6557	72.5	1.8601

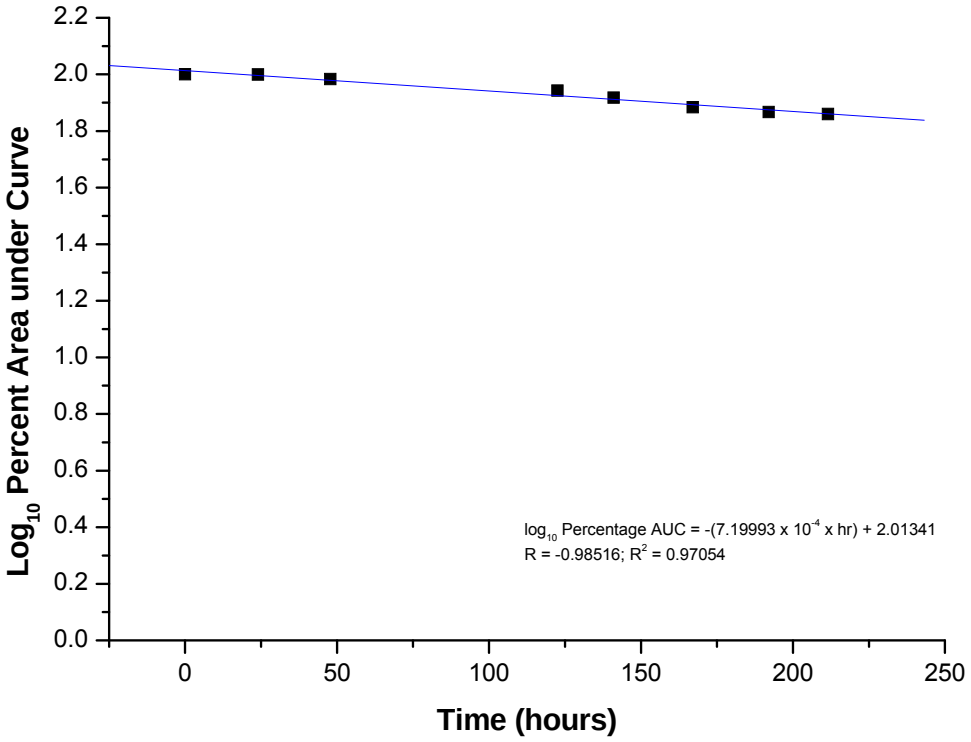


Figure 4-19 -Degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 3.10 (I = 0.5).

Table 4.15 - HPLC data on the degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 4.00

Time (hours)	**pH**	**Peak Area of lincomycin hydrochloride at pH 4.00**	**Log_{10} Peak Area**	**Percentage of baseline AUC**	**Log_{10} Percentage of baseline AUC**
0.0	3.93	6531376	6.8150	100.0	2.0000
24.0	3.95	6365779	6.8039	97.5	1.9890
48.0	3.98	6250963	6.7959	95.7	1.9809
77.0	4.00	6189162	6.7916	94.8	1.9768
96.0	3.99	5908979	6.7715	90.5	1.9566
120.0	3.98	5976058	6.7764	91.5	1.9614
167.0	3.98	5416733	6.7337	82.9	1.9186
216.0	4.00	5387098	6.7314	82.5	1.9165

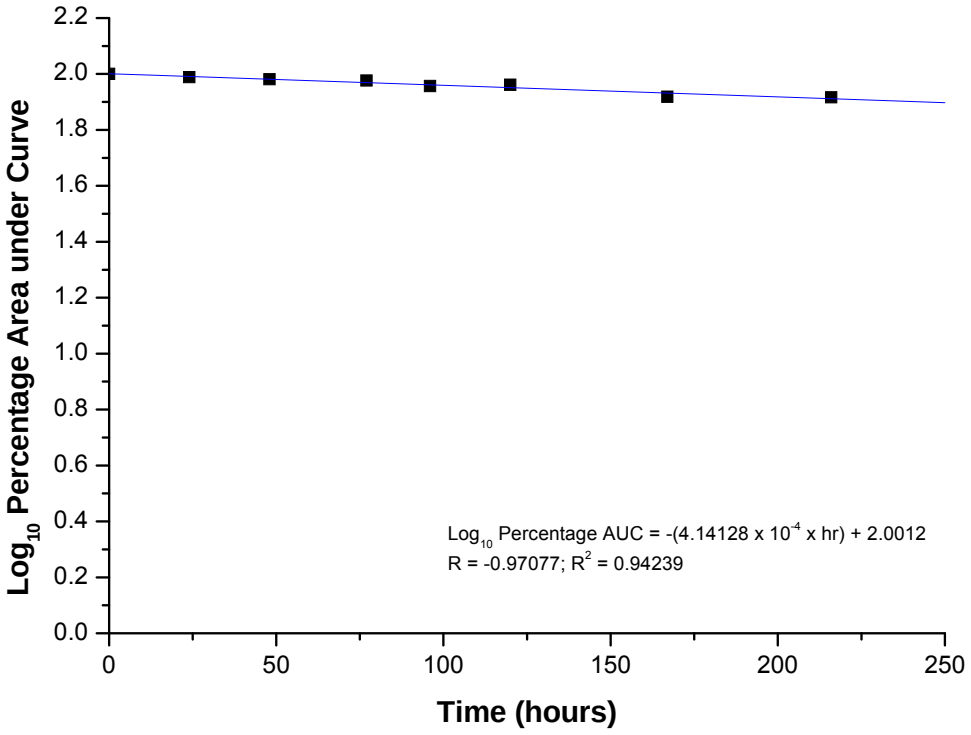


Figure 4-20 -Degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 4.00 (I = 0.5).

Table 4.16 shows the HPLC data of 0.6 mg/mL lincomycin hydrochloride obtained at pH 6.10. The degradation of lincomycin hydrochloride at pH 6.10 is shown graphically in Figure 4.21, which shows $\log_{10}$ area versus time and $\log_{10}$ percent of lincomycin.

Table 4.17 shows the HPLC data of 0.6 mg/mL lincomycin hydrochloride obtained at pH 8.00. The degradation of lincomycin hydrochloride at pH 8.00 is shown graphically in Figure 4.22, which shows $\log_{10}$ area versus time and $\log_{10}$ percent of lincomycin.

Table 4.16 - HPLC data on the degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 6.10

Time (hours)	pH	Peak Area of lincomycin hydrochloride at pH 6.10	Log_{10} Peak Area	Percentage of baseline AUC	Log_{10} Percentage of baseline AUC
0.0	6.09	7203789	6.8576	100.0	2.0000
24.0	6.07	6831139	6.8345	94.8	1.9768
48.0	6.10	5780173	6.7619	80.2	1.9042
72.0	6.14	5464064	6.7375	75.8	1.8797
96.0	6.14	4881498	6.6886	67.8	1.8312
119.0	6.10	4669754	6.6693	64.8	1.8116
142.5	6.12	3834850	6.5837	53.2	1.7259
216.0	6.12	3098224	6.4911	43.0	1.6335

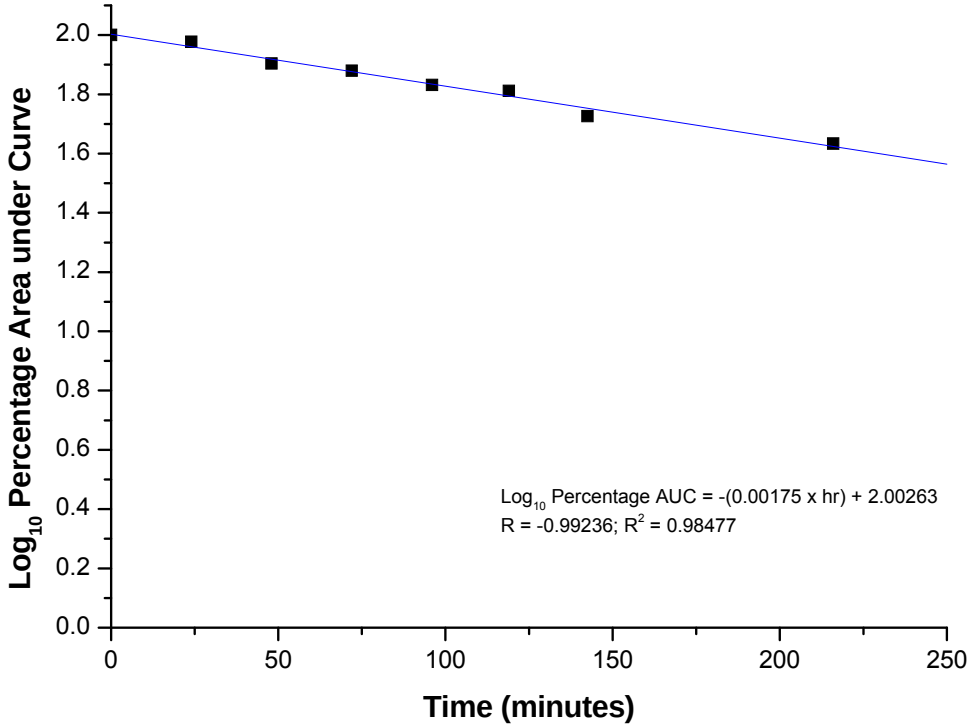


Figure 4-21 -Degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 6.10 (I = 0.5).

Table 4.17 - HPLC data on the degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 8.00

Time (hours)	**pH**	**Peak Area of lincomycin hydrochloride at pH 8.00**	**Log_{10} Peak Area**	**Percentage of baseline AUC**	**Log_{10} Percentage of baseline AUC**
0.0	7.89	6794621	6.8322	100.0	2.0000
24.0	7.89	6256170	6.7963	92.1	1.9643
48.0	7.93	5369299	6.7299	79.0	1.8976
72.0	7.93	4704771	6.6725	69.2	1.8401
96.0	7.92	4191389	6.6224	61.7	1.7903
119.0	7.92	3841709	6.5845	56.5	1.7521
142.5	7.92	3423270	6.5344	50.4	1.7024

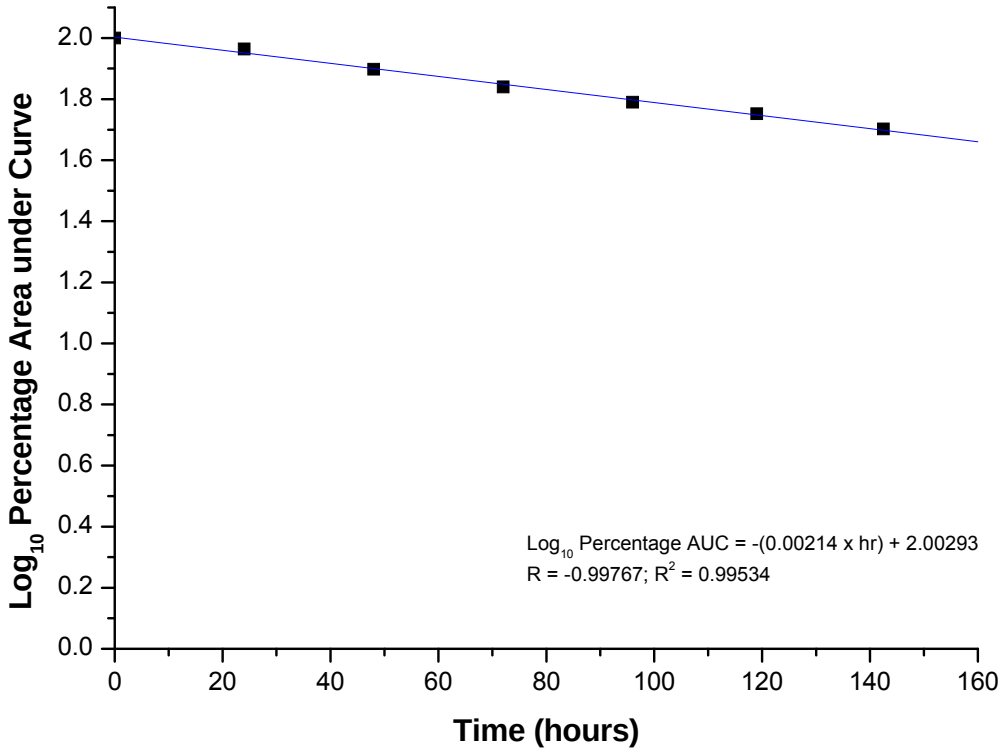


Figure 4-22 -Degradation of 0.6 mg/mL lincomycin hydrochloride at 80°C at pH 8.00 (I = 0.5).

Figure 4.18 to 4.22 show graphic representations of lincomycin hydrochloride degradation at pH 2.00, 3.10, 4.00, 6.10 and 8.00. The calculated rate constant and shelf-life of lincomycin hydrochloride at each pH tested is summarised in Table 4.18. The results show that lincomycin hydrochloride had the greatest stability at pH 4.00 when stored at 80°C, with a calculated shelf-life of 4.59 days. It was least stable at pH 2.00, with a calculated shelf-life of 0.38 hours.

Figure 4.23, which shows the log k: pH profile of lincomycin hydrochloride, also shows that lincomycin hydrochloride was most stable at pH 4.00. Since lincomycin is a basic compound in which the single amine group is tertiary with a pK_a of 7.6[103] at low pH (i.e. pH 2 to 3), it undergoes acid catalysed degradation of the deprotonated form. At higher pH values, from pH 6.10 to 8.00, there is some hydroxyl ion catalysis limited by the protonation occurring in that pH range.

Table 4.18 - Data for lincomycin showing the gradient of equations, correlation coefficient, rate constant and shelf-life obtained at pH 2.00, 3.10, 4.00, 6.10 and 8.00 at 80°C.

pH	Graph Type	Gradient ($m \times 10^{-3}$)	Error ($\times 10^{-5}$)	Coefficient of determination (R^2)	k ($\times 10^{-3}$ $hour^{-1}$)	t_{90} (hours)	t_{90} (days)
2.00	Log_{10} Peak Area	-4.94	6.048	0.99836	11.4	9.23	0.38
	Log_{10} % AUC	-4.94	6.065	0.99834	11.4	9.23	0.38
3.10	Log_{10} Peak Area	-0.72	5.118	0.97058	1.66	63.32	2.64
	Log_{10} % AUC	-0.72	5.12	0.97054	1.66	63.32	2.64
4.00	Log_{10} Peak Area	-0.41	4.144	0.94323	0.95	110.2	4.59
	Log_{10} % AUC	-0.41	4.18	0.94239	0.95	110.1	4.59
6.10	Log_{10} Peak Area	-1.75	8.884	0.98484	4.03	26.05	1.09
	Log_{10} % AUC	-1.75	8.901	0.98477	4.03	26.05	1.09
8.00	Log_{10} Peak Area	-2.14	6.488	0.99543	4.93	21.31	0.89
	Log_{10} % AUC	-2.14	6.544	0.99534	4.93	21.31	0.89

Table 4.19 - Rate constant and log k for lincomycin hydrochloride at pH 2.00, 3.10, 4.00, 6.10 and 8.00 at 80°C

pH	Rate constant (k)	log k
2.00	1.14 x 10-2	-1.943
3.10	1.66 x 10-3	-2.780
4.00	9.53 x 10-4	-3.021
6.10	4.03 x 10-3	-2.395
8.00	4.93 x 10-3	-2.307

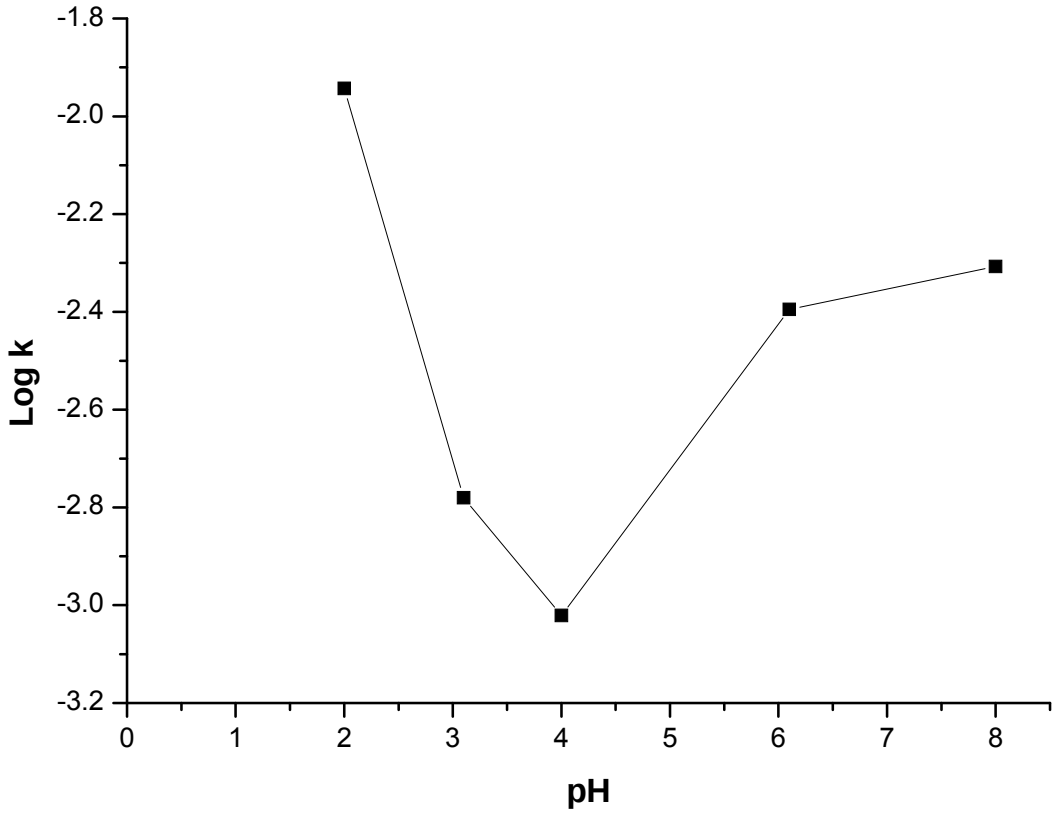


Figure 4-23 -Log k: pH profile of 0.6 mg/mL lincomycin hydrochloride at 80°C.

Chapter 5
Discussion

5.1 Methodology

This is the first randomised 12 month study of all paediatric patients across three hospital settings (inpatients, outpatients and Emergency Department admissions) in Australia and internationally. Other studies have evaluated specific hospital settings, including several in inpatients including a census sample as they presented to the hospital[4, 20, 22, 24, 42, 46, 51] and randomly selected patients only in that setting[55] or another single setting.[69] No previous study has randomly selected patients across all three settings. In this study, data for 1200 records were randomly selected from a total population of 145,550 patients which included 458 patients from 55,591 Emergency Department admissions, 202 patients from 24,425 inpatients and 540 patients from 65,534 outpatients. The reason 1200 random cases were generated was in case some patient files were not available (which was likely for child protection cases and patients being seen at the hospital, as their file would have been in use). The study was powered to identify a two percent difference in major parameters.

This study is the first study undertaken at PMH since that reported by Turner in 1999.[24] Unlike Turner's five week study which involved only a sample of 200 consecutive inpatients (100 from a medical ward and 100 from a surgical ward), this one-year retrospective study involved 1037 randomly selected patients across three hospital settings (inpatients, outpatients and Emergency Department patients).

5.2 Definitions of off-label and unlicensed and their classification

The definitions proposed by Turner for off-label, with some modification to the unlicensed definition, were adopted for this study.[24] The hierarchical classification system for off-label drugs by Hsien et al.[42] was adopted and the approach taken was that an off-label drug cannot be identified in more than one classification. All prescription drugs were initially analysed for age so that drugs with no paediatric information or those prescribed in an age group for

which the drug was not licensed were classified as off-label for age.[42] In keeping with Hsien et al.[42], the next hierarchical level was indication, then route of administration and finally dosage (which included frequency of administration). A hierarchical approach has also been reported in other studies. For example, Ribeiro et al.[69] who only considered drugs for outpatient care, used a mutually exclusive graded approach based on indication, then age, then dose and frequency and finally route of administration. If there was no information regarding its use in the product information, the drug was classified as off-label, most likely due to age similar to Hsien, as only the four classifications of indication, age, dose/ frequency and route of administration were used, although this was not clearly specified.[69]

For ease of analysis, each patient was also classified into either an off-label or unlicensed category. Patients prescribed only off-label drugs and those prescribed both off-label and unlicensed drugs were classified as 'off-label' patients. Patients prescribed only unlicensed drugs were classified as "unlicensed".

Initially, the age classification in the AMH 2008[111], which includes neonates (zero to 28 days), young infants (one to three months), infants (three months to two years) and children (two to 12 years) was considered for use. Notably, this has been changed recently in the AMH 2014[112] to include only three age categories: neonates (zero to 28 days), infants (one month to two years) and children (two to 12 years). Other age classification systems were also considered[48, 54, 57, 61, 64, 68, 113] but the internationally recognised classification system of the European Medicines Agency (EMA)[6] (term newborn infants/ neonates 0 – 27 days, infants and toddlers 28 days - 23 months, children 2 - 11 years, adolescents 12 - 18 years), used by Hsien et al. and other researchers[42, 50, 55, 69] was adopted for this study. Some researchers used the EMA age classification but further divided the 2-11 years group into 2-5 years (preschool) and 6-11 years (school children) as they reported it reflects more accurately a child's ability to take solid drug formulations.[67] This was not

adopted for the current study as the EMA classification provides the best option for standardisation and is harmonised with the TGA.

5.3 Factors influencing off-label and unlicensed prescribing in Australia

The majority of patients included in this study (58.5%) were males, which was similar to previous findings at PMH by Turner[24] who reported 61.5% of males (i.e. 58% in surgical ward and 65% in medical ward) and another Australian study in Tasmania which reported 56% of males.[62] The age of paediatric patients ranged from zero (newborn) to 18 years (mean 6.6 $\pm$ 5.2 years). The youngest patient was a newborn admitted as an inpatient and the oldest patient, aged 18.4 years, was an outpatient. The mean and median ages varied across the three settings (Emergency Department patients 5.6 / 4.0 years, inpatients 6.4 / 5.4 years, outpatients 7.8 / 7.8 years respectively), with Emergency Department patients generally younger than outpatients ($p = 0.0003$). In Turner's study[24] the age ranged from 49 days to 18 years (median 6 years). The median age of inpatients in this study (5.4 years) was comparable to that reported by Turner .[24]

Of the three hospital settings investigated, the majority of patients (38.9%) were Emergency Department admissions. In each setting there were more males than females. The highest numbers of admissions in the Emergency Department were for patients under three years of age and inpatients less than one year of age. The age distribution of outpatients did not show peaks as seen for emergency patients and inpatients, although there were a greater percentage of patients less than two years of age and also between nine and ten years.

There were 2654 prescribed drugs of which 1905 (71.8%) were licensed, 681 (25.7%) were off-label and 68 (2.6%) were unlicensed, hence the overall extent of off-label and unlicensed prescribing was 28.3%. In comparison to other Australian studies, this was higher than the 16.2% reported by Turner

in the 1999 PMH study[24] but lower than the 47% reported by O'Donnell.[1] The extent of off-label and unlicensed prescribing was slightly higher in inpatients in the current study (30.7%) compared to Turner and was similar to a recent inpatient study in Tasmania which reported the extent of off-label prescribing as 31.8%.[62] The study by O'Donnell was conducted in an Australian neonatal intensive care unit and involved patients with a gestational age of 22.7 to 41.4 weeks.[1] The difference in the age of patients in O'Donnell's study and other Australian studies involving older patients, such as Turner's study (in which the age ranged from 49 days to 18 years), Ballard's study (in which the age ranged from one day to 11 years) and the current study (age zero to 18.4 years), makes a direct comparison erroneous.[1, 24, 62] However, in the current study, when only inpatient neonates aged zero to 27 days were considered, despite some being slightly older than in O'Donnell's study, the extent of off-label prescribing was 83.3% (Table 3.15) which was considerably higher than the overall study result. Although the number of inpatients in this group was small (n = 12), the finding suggests that by targeting specific patient groups, including specific age groups, the extent of off-label prescribing reported can increase considerably. In addition, by limiting age range to lower age groups will give a higher likelihood of off-label classification, especially with respect to age.

Inpatients were prescribed between zero and 21 drugs (emergency patients between zero and 16 drugs and outpatients between zero and 12 drugs). The median number of drugs prescribed was one drug for both emergency patients and outpatients and five drugs for inpatients (overall study median was one drug). One reason for a higher median number of drugs for inpatients was that very few patients were prescribed no drugs (4.7%) compared to Emergency Department patients (38.0%) and outpatients (45.5%). This was similar to Ballard's inpatient study in Tasmania, in which only 20 of 300 patients (6.7%) were prescribed no drugs. The difference in the number of drugs prescribed in each setting was significant ($p < 0.0001$). The overall median in this study was lower than the median of four drugs reported by Turner. However, Turner's study was conducted on inpatients and in this study, when only inpatients were considered, the median number

of drugs (five) was slightly higher than reported by Turner (four).[24] A contributing factor to these differences may be that Turner's study involved only two wards (a surgical and medical ward) whereas in this study, patients were randomly selected from all inpatient wards at PMH.

Overall, 699 (67.4%) patients were prescribed drugs, which included 321 (31.0%) patients prescribed licensed drugs and 378 (36.5%) that were prescribed off-label or unlicensed drugs. Three hundred and thirty eight patients (32.6%) were not prescribed any drugs. The percentage of patients prescribed off-label or unlicensed drugs (36.5%) was similar to Turner's study which reported that 36% of patients received off-label or unregistered drugs.[24] In the current study, when patients who were not prescribed drugs were excluded, the extent of off-label and unlicensed prescribing would have been 54.1% (i.e. 378 / 699). However, in the current study, when only inpatients were considered, the number of patients prescribed off-label or unlicensed drugs increased significantly to 77.6% (77.8% for males and 77.3% for females). The percentages were much lower for Emergency Department patients (29% of males and 27% of females) and outpatients (19% of males and 17% of females). The differences in the number of patients prescribed off-label and unlicensed drugs in different settings was significant ($P < 0.0001$). The extent of off-label and unlicensed prescribing to inpatients in the current study was higher than in Ballard's retrospective inpatient study which reported that 57.3% of patients received at least one off-label medicine. One reason is that Ballard's study only considered off-label drugs and not unlicensed drugs.[62] Another possible reason is that Ballard's study included patients aged one day to 11 years whereas the current study included paediatric patients aged zero to 18 years.[62] Ballard also excluded unscheduled over-the-counter (OTC) medications which were not excluded in the current study. Although paracetamol is an OTC medication, this was included in Ballard's study contradicting the exclusion criteria set for that study.

In the current study, there were 330 different drugs which included 121 different off-label drugs and 22 different unlicensed drugs. In considering only

inpatients, 82 different off-label drugs and 14 different unlicensed drugs were prescribed. Turner reported that 86 different drugs were used in the surgical ward (of which 22 drugs were off-label or unlicensed) and 118 different drugs in the medical ward (of which 35 drugs were off-label or unlicensed).[24] Turner does not specify whether prescribed drugs, including off-label and unlicensed drugs, were similar on both wards (i.e. whether there was overlap) or whether they were entirely different drugs. There is insufficient information provided by the author to enable this to be further analysed.[24] However, the number of different off-label or unlicensed drugs prescribed in the current study was higher than reported by Turner.[24] It was also higher than the findings in Tasmania[62] where researchers reported that out of 887 drug prescriptions, there were 51 different off-label drugs (out of 106 different drugs). A reason for reporting fewer different off-label drugs in Ballard's study may be that unscheduled products were excluded which may have contributed to a decrease in the range of medications. A likely reason for a greater number of different off-label drugs reported in the current study compared to the previous PMH study is that drugs used off-label across all wards were identified rather than findings reported for only two wards, as in Turner's study.

The ten most commonly prescribed drugs were paracetamol, ibuprofen, ondansetron, Painstop Day®, morphine, oxycodone, amoxicillin, dexamethasone, salbutamol and prednisolone, half of which are analgesics/ antipyretics from the nervous system ATC code (paracetamol, ibuprofen, Painstop Day®, morphine and oxycodone). Prednisolone was not used in an off-label or unlicensed manner on any occasion. The two most commonly prescribed drugs (paracetamol and ibuprofen) were the same as reported in Ballard's study but unlike Ballard who reported oxycodone as the third most commonly prescribed drug, in this study the third most commonly prescribed drug was ondansetron (which was also the most commonly prescribed off-label drug).[62] Turner reported that paracetamol was also commonly prescribed on both the medical and surgical ward but not ibuprofen. Other drugs commonly prescribed on the medical ward in Turner's study included salbutamol, ceftriaxone, prednisolone and on the surgical ward, morphine,

metronidazole and ceftriaxone.[24] In the current study, morphine, salbutamol and prednisolone were also most commonly prescribed but not ceftriaxone and metronidazole.

The 10 most commonly prescribed off-label drugs overall were ondansetron, Painstop Day®, salbutamol, oxycodone, paracetamol, midazolam, fentanyl, ticarcillin with clavulanic (Timentin®), amoxicillin and flucloxacillin. Most of these drugs were nervous system drugs (Painstop Day®, oxycodone, paracetamol, midazolam, fentanyl) and anti-infectives (Timentin®, amoxicillin, flucloxacillin). Turner reported the most commonly prescribed off-label and unlicensed drugs were metoclopramide, Colonlytely®, ondansetron, clonidine and chloral hydrate, although there were differences on the wards.[24] On the surgical ward, the drugs were metoclopramide, Colonlytely®, ondansetron, clonidine and on the medical ward they were chloral hydrate, aspirin, ciprofloxacin and sodium bicarbonate. Despite considerable differences between Turner's findings and those reported in the current study, ondansetron was commonly prescribed off-label in both studies.[24] However, in Turner's study, ondansetron was reported off-label for indication but in the current study it was off-label for indication, age and dosage although age was the first factor employed for the classification.[24]

Ballard et al reported the most commonly used off-label drugs as oxycodone, salbutamol, paracetamol, ondansetron and amoxicillin, with oxycodone used off-label more frequently than any other drug.[62] Although these drugs are in the top five most commonly prescribed off-label drugs in the current study, unlike Ballard, ondansetron was the most commonly prescribed off-label drug. It was prescribed a total of 126 times of which 94 prescriptions (74.6%) were off-label. Reasons for off-label prescribing included dosage (65; 69.2%), age (16; 17.0%) and indication (13; 13.8%).

Several different dosage forms of ondansetron have TGA marketing approval including injections, tablets, wafers, syrup and suppositories. All dosage forms are approved for the prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy. The injection is also

approved for prevention and treatment of postoperative nausea and vomiting (PONV). Ondansetron suppositories are not recommended for children and in this study there were no prescriptions for ondansetron suppositories. For emetogenic chemotherapy or radiotherapy, ondansetron injection, tablets, wafers or syrup are licensed for children over four years of age at a dose of 5 mg/ m^2, followed by oral therapy at doses of 4 mg twice daily up to five days. For prevention and treatment of PONV, ondansetron injection only is licensed for children aged two to 12 years of age at a dose of 0.1 mg/ kg up to a maximum of 4 mg. Although not specified in the PI, at 12 years of age it is assumed the adult dose is used.[30]

In this study, several children were prescribed ondansetron for PONV to be administered three to four times a day and often on a "when required" basis despite MIMS stating that repeat dosing has not been studied in paediatric patients.[30, 108] In a few cases, oral forms of ondansetron were prescribed for PONV instead of the approved injection. None of the oral forms (tablets, wafers, syrup) are approved for PONV.

Although not indicated for children under two year of age because the clinical safety in this age group has not been established,[30, 108] ondansetron was prescribed to 13 children under two years of age with the youngest two infants three months old. Ondansetron syrup, which is only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting in children older than 4 years, was prescribed to three other children aged two and three years. The diagnosis in the medical records was cystic swelling to the neck and infective exacerbation for a two year old child, dental trauma and extraction for another two year old child and spinal fracture for a three year old child. As there was no indication that any of the children were undergoing cytotoxic chemotherapy or radiotherapy, ondansetron was most likely used for PONV, also rendering it off-label for indication. According to the hierarchical classification outlined in Chapter two in section 2.4.1, for these children ondansetron syrup was classified off-label for age, although it was also off-label for indication. In some countries, ondansetron is approved for use in children from one month of age for both PONV and chemotherapy

induced nausea and vomiting (CINV).[65] Recently the TGA listing in Australia for Zofran® (which contains the single ingredient ondansetron), was updated with information stating that the IV form can be administered to children from one month onwards for PONV[107] but at the time of writing, MIMS 2014 had not been updated to reflect this information.[30] The fact that ondansetron can be used for PONV and CINV in some overseas countries but in Australia, only the injection can be used in children over one month of age for PONV highlights the inconsistency in PIs on an international platform.

Painstop Day®, which contains a combination of 120mg paracetamol and 5 mg codeine phosphate per 5 mL, was the second most commonly prescribed off-label drug. It was off-label for 89% of cases due to higher doses of Painstop Day® prescribed than recommended by the approved license. In the majority of cases, the increase in dose ranged from 17% to 75%. A few obese children were prescribed higher doses than this. In one case, an eight year old Emergency Department male patient weighing 42.9 kg, with an infection and inflammation of the little toe and boil like lesions on the inner aspects of the thigh, was prescribed double the normal dose for age (i.e. 30 mL rather than 13 to 15 mL recommended for children aged eight to nine years). The average weight for boys aged eight years is 25.8 kg and for boys aged nine years, it is 28.7 kg,[37] so it is likely that this 42.9 kg child was overweight, although it was not possible to calculate the BMI as height was not recorded in the medication chart. A dose of 30 mL Painstop Day® provides 720 mg paracetamol and 30 mg codeine. If the paracetamol dose was calculated based on 15 mg/kg and the child's weight of 42.9 kg, then the dose would have been 644 mg. If the paracetamol dose was calculated based on ideal body weight for a child eight years of age (i.e. 25.8 kg), then the dose would have been 387 mg paracetamol. However, the child was prescribed 720 mg paracetamol which is considerably greater than recommended.[30]

In another case involving a nine year old female with a slipped femoral epiphysis and weighing 44.4 kg, a dose of 35 mL was administered despite the manufacturer's recommended dose of 15 mL for children aged nine to 10

years. This child received more than double the recommended dose. All doses for Painstop Day® specified in MIMS[30] are for children of certain ages and corresponding weights [i.e. Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL]. Although it may be challenging for a health practitioner to adhere to the recommended dose for obese patients, especially if they are in considerable pain, obesity does not necessarily translate to a more active liver to detoxify drugs or more active kidneys to aid elimination.

Ballard did not report off-label use associated with Painstop Day® but this may be because the researchers excluded over-the-counter (OTC) medication in their study.[62]

Paracetamol was also commonly prescribed off-label - it was the fifth most commonly prescribed off-label drug. The standard dose of 15 mg/kg/dose in the accepted license[30] was exceeded in 15.3% of prescriptions (dose range 17 mg/kg/dose to 30 mg/kg/dose). The extent of off-label use of paracetamol was similar to the 10% reported by Ballard in which paracetamol was used at approximately 20 mg/kg/dose. In the current study, it was found that the maximum daily dose prescribed was up to 81 mg/kg/day. This was also comparable to Ballard's study which reported that up to 80 mg/kg/day paracetamol was prescribed.[62] Although doses above 15 mg/kg/dose are not listed in the approved paracetamol license, standard references such as the Paediatric Pharmacopoeia (Royal Children's Hospital, Melbourne)[114] and the AMH[111, 112] state that up to 90 mg/kg/day can be used under medical supervision, to be reviewed at 48 hours. The AMH specifies that this dose recommendation is for children older than three months.[111, 112] However, there are reports in the literature of hepatic failure in children when doses greater than 75 mg/kg/day were administered.[115] There are currently no published case-control or population based studies of repeated supratherapeutic doses of paracetamol and this should prompt an organised study to be considered to determine definitive recommendations.[115]

Both the AMH and Paediatric Pharmacopoeia reflect current best practice in Australia but include many recommendations that involve the use of off-label medicines when compared to the manufacturer's product information. There clearly needs to be a mechanism by which the product license is updated regularly, especially for children, with evidence based professional recommendations.

Salbutamol was prescribed 58 times and was off-label 51 times (87.9%) because it was prescribed at doses or frequencies greater than that stated in the approved license (one to two inhalations repeated four hourly if needed). In many cases, the prescribed dose was six inhalations at various dose intervals, in some cases including every 20 minutes. Ballard also reported that salbutamol was commonly off-label due to higher dosages than those approved.[62] The National Asthma Council's First Aid Protocol and the Asthma Management Handbook[116], as well as other references,[111, 112] support the use of increased dosages of salbutamol, despite not being reflected in the PI.

There were 74 prescriptions for oxycodone, of which 49 (66%) were classified off-label. This is less than reported in Ballard's study where it was found that oxycodone was used off-label in all cases. Although Ballard reported that the PI of both oxycodone liquid and tablet dosage forms stated that "the drug should not be used in patients under 18 years of age" there was no evidence found in the approved license to support this.[62] In the current study, it was found that the PI for oxycodone (OxyNorm®) capsules, liquid and injection stated it should not be used in patients under 18 years of age whereas the controlled release tablets (OxyContin®) were not recommended in children under 12 years of age.[30] As Ballard's study excluded children aged 12 years or older, regardless of which oxycodone dosage form was administered in the Tasmanian study, it would have been classified as off-label due to age.[62]

In the current study, most children prescribed oxycodone were aged under 12 years with the youngest, both a male and a female, aged 10 months.

There are reports in the literature that oxycodone may provide superior pain relief to some other analgesics.[117, 118] Several studies have investigated the pharmacokinetics of oxycodone in children. One study in children aged six months to seven years reported that a weight-based dose without adjustment for age between six months and seven years was valuable[119] while another study that investigated the pharmacokinetics of oxycodone in infants aged zero to six months, reported pronounced variability in clearance and half-life in the young children and recommended that routine dosing of oxycodone in young children may be dangerous.[120] Although oxycodone has been in clinical use for 90 years, the PI does not include directions for use in children. A large clinical study should be undertaken involving various paediatric age groups and the PI updated to reflect appropriate dosage guidelines for children.

Midazolam was commonly prescribed in an off-label manner which was a finding not reported in other Australian studies.[1, 24, 62] It was prescribed 31 times and of these, 29 (93.5%) prescriptions were off-label. Following the hierarchy discussed in Chapter two (section 2.5.1), 20 midazolam prescriptions were off-label for age because the drug was prescribed to children under the age of eight years, the youngest being a newborn. MIMS states that the "safety and effectiveness of midazolam in children below the age of eight have not been established". The other nine prescriptions were off-label for route of administration, since midazolam solution for injection was administered buccally to children older than eight years of age. Although according to the classification system used in this study based on Hsien that a drug can only be classified into one off-label category, if further classifications had been used in this study, then of the 20 prescriptions that were off-label for age, 11 prescriptions were also off-label for route of administration since midazolam solution for injection was administered buccally.

Fentanyl, an opioid with a rapid onset of action and short duration of action, is available as solution for injection or patch for transdermal delivery. It was prescribed 39 times of which 21 (53.8%) were off-label. In one case, fentanyl

was prescribed to a one-year old child and hence was off-label for age because MIMS states that "the safety of fentanyl in children younger than two years of age has not been established".[30, 108] For the other 20 cases, fentanyl was off-label due to route of administration since the solution for injection was administered intranasally. There is no information in the PI to support this route of administration. However, the AMH recommends an intranasal dose for children aged one to 12 years and advises that if the 100 mcg/2 mL injection solution is used, that the dose should be divided between nostrils to minimise swallowing and effects such as sneezing.[111, 112] Fentanyl is not available as an oral dosage form and while the intravenous and intramuscular routes are effective, they require painful placement of intravenous lines or injections. Advantages of fentanyl are that it has fewer cardiovascular effects than other opioids and does not cause histamine release.[121] Several randomised controlled trials have shown that intranasal fentanyl is equivalent or superior to fentanyl administered parenterally or morphine administered parenterally or orally in providing analgesia for various painful procedures and conditions in children. Evidence for the use of intranasal fentanyl in children has been available since 1999 yet despite this, the PI has not been updated to reflect this.[121]

Timentin® (ticarcillin with clavulanic acid) was prescribed 19 times and was off label for age in 95.0% of prescriptions. MIMS states that "the efficacy and safety of Timentin® has not been established in infants and children under the age of 14". The youngest child prescribed Timentin® was a 10 month old male. Timentin® was not reported to be commonly prescribed off-label (in the top 10 drugs) in any other Australian study.

The two most commonly prescribed unlicensed drugs were dexamethasone and dilacaine. PMH produces hospital formulations of dilacaine eye drops and dexamethasone oral solution (1mg/mL). Dilacaine eye drops contain proxymetacaine HCl 1.25mg, cyclopentolate HCl 2.5mg, tropicamide 2.5mg, phenylephrine HCl 25mg and are used as mydriatic and anaesthetic eye drop for examination of the fundus of the eye. Dexamethasone, a synthetic glucocorticoid with anti-inflammatory or immunosuppressive actions, is also

used in neonates for respiratory insufficiency and oedema with acute non-infectious laryngospasm. Neither of these drugs were reported off-label in Turner's or O'Donnell's study. As Ballard's study involved only off-label drugs, no unlicensed drugs were included.[62]

5.4 Variations in prescribing with age

Neither Turner nor Ballard identified drugs commonly prescribed to different age groups. In this study, the 10 most commonly prescribed drugs overall were different for various age groups. Seven out of 10 drugs for neonates aged zero to 27 days were from the ATC anti-infective classification and included amoxicillin, gentamicin, cefotaxime, nystatin, aciclovir, Augmentin Duo® and vancomycin whereas only three anti-infectives were included in the 10 most commonly prescribed drugs for infants aged 27 days to 23 months (amoxicillin, flucloxacillin and Augmentin Duo®), one for children aged two to 11 years (amoxicillin) and none for adolescents. Seven out of the 10 most common drugs for adolescents aged 12 to 18 years were from the ATC class nervous system (paracetamol, ibuprofen, oxycodone, morphine, Panadeine Forte®, Panadeine® and fentanyl) and alimentary tract (ondansetron). Six of the most common drugs prescribed for children aged two to 11 were the same as those prescribed for adolescents except instead of Panadeine Forte® and Panadeine®, Painstop Day® was more commonly prescribed.

5.5 Variations in off-label and unlicensed prescribing with age

There were also variations in the 10 most commonly prescribed off-label drugs for various age groups. For example, newborn infants aged zero to 27 days were prescribed more anti-infectives than any other age group with seven out of 10 drugs from the ATC anti-infective classification. The most commonly prescribed off-label anti-infectives to newborn infants were amoxicillin, gentamicin, and aciclovir.

For age groups other than neonates, more nervous system drugs were prescribed off-label. Differences were noted for the types of nervous system drugs prescribed off-label to the different age groups. Infants (27 days to 23 months) and children (two to 11 years) were prescribed mainly off-label analgesics but adolescents were prescribed more diverse nervous system drugs including off-label analgesics, sedatives, hypnotics and other psychotherapeutic drugs including fluoxetine and quetiapine.

Turner reported that metoclopramide and clonidine were commonly prescribed off-label (metoclopramide for dose and clonidine for indication).[24] Although these two drugs were not in the ten most commonly prescribed off-label drugs in the current study, they were in the top 10 off-label drugs prescribed to children aged two to 11 years, but not for any other age group. In this study, as in Turner's study, clonidine was off-label for indication.[24] However, unlike Turner's study, in the current study, metoclopramide was off-label for age. MIMS states the use of metoclopramide should be restricted in children and young adults less than 20 years of age to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs and to assist in small bowel intubation[30, 108] and since there was no evidence that any of the patients met these criteria, metoclopramide was classified off-label for age. It could, however, have been classified as off-label for indication but as a result of the hierarchical approach used in this study and since all children prescribed metoclopramide were under the age of 20 years, metoclopramide was classified off-label for age.

5.6 Specific prescribing issues in neonates

Amoxicillin was the most commonly prescribed off-label drug to neonates aged zero to 27 days. The dose for amoxicillin specified in eMIMS for children less than 20 kg is 20 to 40mg/kg/day in divided doses every six to eight hours. For the majority of patients, a greater dose was prescribed than specified in the PI. In one case, amoxicillin was prescribed at a higher dose

for possible viral meningitis, so it was off-label for dose and indication, although using the hierarchical approach, it was classified off-label for indication.

Aciclovir was prescribed to two newborn infants and one four week old infant despite no dosage listed in eMIMs.[30] Two of the infants had suspected viral meningitis. The notes for the third infant did not specify why aciclovir was prescribed, but the diagnosis of hypoxic ischaemic neonatal encephalopathy with meconium aspiration and seizures could suggest that it was used prophylactically to prevent viral infection. Intravenous dosing information is provided in eMIMs for children aged one to 12 years for the treatment of herpes simplex encephalitis but not for its prevention.[30] The recommended dose for children aged one to 12 years of age with herpes simplex infections (except herpes simplex encephalitis) or varicella zoster infections is 250 mg/ m^2 of body surface area (equivalent to 5 mg/ kg in adults) and for herpes simplex encephalitis is 500 mg/ m^2 of body surface area (equivalent to 10 mg/ kg in adults). No dose is provided for children less than one year of age.[30] Indications of aciclovir listed in the AMH include treatment as well as prevention of herpes simplex infections. Notably, a dose for infants less than three months for herpes simplex (based on body weight (20 mg/ kg IV every 8 or 12 to 24 hours depending on whether the infant is preterm or term)) is provided in the AMH 2013 but not AMH 2014.[112, 122] The dose for children aged three months to 12 years for herpes simplex encephalitis in both references is 500 mg/ m^2 every eight hours.[112, 122] However, the Therapeutic Guidelines (Antibiotics) recommends a dose of 20 mg/ kg aciclovir for suspected or proven herpes simplex encephalitis, administered IV, eight hourly for 21 days with the dose adjusted for renal function.[123] For babies under three months, the Paediatric Pharmacopoeia provides a dose of 20 mg/ kg 12 to 24 hourly (preterm) and eight hourly for term infants.[114] The new AMH Children's Dosing Companion 2013 lists the same dose for infants from birth (term) to three months although the dose provided for encephalitis is 500 mg/ m^2 every eight hours.[99]

Gentamicin, an aminoglycoside antibiotic, was also commonly prescribed off-label for neonates aged zero to 27 days. The dose for gentamicin specified in the PI for life threatening infections is five to 7.5 mg/ kg/ day administered in two to three divided doses.[30] Three cases were off-label due to frequency of administration of the dose - for two cases the dose was administered once daily and for the other case, the dose was initially administered every two days and then once daily. For the other case, the dose administered was 21 mg every 2.5 hours which equated to 45 mg/kg/day, thereby exceeding the recommended dose.

In Ballard's study, gentamicin was always used in an off-label manner which was not the finding in the current study.[62] However, as outlined in Chapter two, where there was any uncertainty with respect to dosing, frequency of dosing or indication, a conservative approach was adopted and the drug classified as licensed. There may have been more off-label gentamicin cases in the current study but the frequency of administration and indication was not always clear on the medication chart so it is likely that the extent of off-label use has been under reported. The PI in eMIMS only details divided daily doses and in Ballard's study it was found single daily doses were administered.[30, 62] Administration of single daily dosing has been supported in the literature for over 15 years as it may decrease the likelihood of nephrotoxicity and ototoxicity in children, but despite this, the PI has not been updated.

In one study in the UK, researchers reported that gentamicin was commonly used off-label in many neonatal centres. They reported that if twice daily doses were used as recommended by the manufacturer, premature infants would be exposed to excessive serum concentrations. The reason for this is that the drug is renally excreted and at birth renal function in limited due to immaturity of the kidney, hence in these infants, gentamicin is usually administered at 18 or 24 hour intervals.[43]

5.7 Comparison with international studies

The proportion of off-label and unlicensed prescribing in this study (25.7% and 2.6% respectively) was lower than that reported in several overseas studies in the United Kingdom[43] (55% and 10%), in the United Kingdom, Sweden, Italy, Germany, Netherlands[124] (39% and 7%), in the Netherlands[54] (44% and 28%), Switzerland[55] (25% and 24%), in France[44] (63% and 10%), in Israel[45] (59% and 16%) and in Malaysia[56] (34% and 27%). However, the percentage of off-label prescribing was similar to that reported by Hsien et al. in Germany, who reported off-label prescribing as 30.5%.[42] Several other studies have reported a low incidence of off-label or unlicensed prescribing including a study in Israel[66] (26% and 8%), in the United Kingdom[22] (18% and 7%) and in Croatia[57](12% and 13%). A contributing factor to the lower percentages of off-label and unlicensed prescribing reported in the current study may be that data were collected and combined across all settings at PMH. Most studies, including studies in Australia, have been conducted in one particular setting e.g. Emergency Department patients[64, 65, 69], medical or surgical wards[22, 24, 25, 49, 124] or ICU[1, 42, 43, 45, 56, 59] or outpatients[66, 67]. This renders the comparisons above inappropriate because of the various natures of the patient groups and sites chosen for evaluation. This is an important issue in the reporting of these data.

5.8 Prescribed drugs overseas

Several of the drugs commonly prescribed in the current study were also commonly prescribed in overseas studies including paracetamol[4, 20, 22, 25, 49, 51, 53, 55, 69, 125], ibuprofen[4, 25, 49, 69], morphine[22, 49, 51, 55], oxycodone[20] and salbutamol[69, 124]. In a study across five European countries, Conroy et al.[124] reported that paracetamol was the most widely prescribed drug in four of the five centres included in their study and salbutamol was also a commonly prescribed drug, both of which are in keeping with the current study.

In studies conducted overseas, several of the most commonly prescribed drugs were also prescribed in an off-label manner, including paracetamol[63, 69] and salbutamol[63, 69]. This is similar to the current study. For example, in a study by Conroy et al. involving five European countries, paracetamol was commonly used in an off-label manner in three of the centres investigated and salbutamol was commonly used off-label in four of the centres investigated.[124] Although the reason for the off-label use of paracetamol was not specified in Conroy's study, salbutamol was reported off-label because it was used more frequently than recommended in the approved license. In the current study, paracetamol, which was the most commonly prescribed drug overall, was prescribed off-label in 48 (15.3%) out of 313 prescriptions. However, salbutamol, which was the ninth most commonly prescribed drug, was used off label in 51 (87.9%) of 58 prescriptions. All off-label cases of salbutamol related to dosage, which was similar to Conroy. Paracetamol was also off-label due to dose. Paracetamol[25, 49, 54]and other drugs commonly prescribed off-label in overseas studies included ondansetron[48, 55, 65], salbutamol[54, 66, 67, 69], morphine[49, 53, 124], oxycodone[125], midazolam[64, 125] and fentanyl.[125] In one study, researchers did not specify which drugs were commonly prescribed in an off-label or unlicensed manner so it was not possible to make drug-based comparisons.[56]

Similar to the findings reported by Hsien et al.[42], in the current study the four most frequently prescribed drug groups were analgesics and antipyretics (i.e. nervous system drugs), drugs for the alimentary tract and metabolism, anti-infectives and drugs for the respiratory system.

5.9 Reasons for off-label and unlicensed prescribing in overseas studies

Hsien et al.[42] reported the most common reason for off-label prescribing was dose (39%) which was also found in the current study (47.6%). Other reasons for off-label prescribing reported by Hsien et al.[42] included indication (31%) and age (30%). Hsien et al.[42] did not report any drugs as off-label for

route of administration. In the current study, fewer drugs were off-label due to indication (7.9%) but more drugs were off-label due to age (38.5%) and some drugs were off-label due to route of administration (6.0%).

Many other researchers also reported that the most common reason for off-label prescribing was dose and/ or dose frequency including a recent study in Tasmania.[25, 43, 46, 49, 53, 54, 59, 62, 63, 66, 69, 124] Although in the current study the percentage of off-label prescribing due to dose or dose frequency was 47.6%, this percentage may have been higher but since the hierarchical classification by Hsien et al. [42] was used, once drugs were classified into a category above dosage (i.e. age, indication and route of administration) they were then not considered for another category. Other categories of off-label prescribing in the current study included age (38.5%), indication 7.9%) and route of administration (6.0%)

Some researchers have reported dose and dose frequency as two separate categories. For example, Ribeiro et al.[69] reported that the main reason for off-label prescribing was dosage (28.2%), followed by age (27.8%), indication (23.1%) and frequency of drug use (20.9%). In the current study, as with other studies[62] dosage was defined as including the frequency of drugs administration as well as the dosage given. Following this definition, off-label prescribing in Ribeiro's study equates to 49.1%.[69] However, it is the variations in definition of the term off-label that makes a direct comparison between studies often inappropriate.

Several studies have reported the main reason for off-label prescribing as age.[48, 56] In a study in Malaysia[56] medicines prescribed outside the licensed age range were reported as the most common reason for off-label prescribing (37.1%), followed by dose (21.3%) and indication (19.9%). In this eight week study, which included preterm babies to patients aged under 18 years admitted to a NICU, paediatric ICU, and paediatric high dependency unit, the median age was two years and the highest percentage of off-label and unlicensed prescriptions was for patients in NICU (i.e. patients with a gestational age less than 37 weeks and up to 27 days). It is not surprising

that the most common reason for off-label prescribing in the study was due to age since few medicines are licensed for use in neonates. The results of the study also highlight that the age of the study population can influence reasons for off-label and unlicensed prescribing since the researchers also reported that children younger than two years of age were more likely to receive an unlicensed medicine compared to older children.

Age was also the main reason for off-label prescribing in a recent study in Spain.[48] Researchers reported that in 82.7% of cases, the age range was not covered by the PI (which in Spain is called the SPC i.e. Summary of Product Characteristics) - either by not being directly included in the indication wording or indirectly through the inclusion of specific age-adapted posology recommendations. The other reason for off-label prescribing related to dosage (17.3%) with higher or lower doses prescribed than those recommended.[48]

Due to different definitions of off-label and unlicensed prescribing used in various studies, in another study[59] researchers reported that the most frequent reason for unlicensed medications was that "safety and efficacy have not been established in children". Most other researchers have classified this situation as off-label rather than unlicensed.

5.10 Differences in study design

The percentage of off-label and unlicensed prescribing varies widely between studies, ranging from 16 to 75% of prescriptions and reaching a prevalence of up to 100% when patients that received at least one off-label or unlicensed drug are considered. This variability may be explained by differences in study design, including the selection of different age groups, settings (inpatients, outpatients and Emergency Department patients), the duration of the study, whether the study was retrospective or prospective, different definitions of off-label and unlicensed drugs, different countries and different authorisation

status of drugs in different countries. Some of these differences make a direct comparison between studies inappropriate.

Some studies were retrospective[47, 61, 62, 64-69] but most were prospective studies that varied in the way patients were selected.[1, 4, 11, 22-25, 42, 43, 45, 46, 49-51, 53, 55-57, 59, 60, 63, 124] In many studies data were collected for prescription records of all patients admitted to the study ward within a specified time frame over several consecutive weeks.[11, 22, 42, 46, 53, 54, 56, 60, 63, 124] In a few studies however, data were collected intermittently over a period of time. For example, Palcevski et al.[57] collected data on one predetermined day each month during a 12 month period, Craig et al.[25] collected data on one day each week over a two month period and in a four month study by Barr et al. [45] medications were reviewed every two weeks. In a study in the Netherlands [54], drugs prescribed to children on four different wards were studied for one day each week for five consecutive weeks but on a different day each week. Very few studies were randomised, with most prospective studies collecting data as patients presented to the setting where the study occurred. However, in a randomised study involving five different hospital wards in Switzerland[55], medications prescribed to 60 randomly chosen paediatric patients were studied over a 24 hour period. In a retrospective study in Portugal, Ribeiro et al.[69] randomly selected 700 children for inclusion in the study. It is unknown whether knowledge that a prospective study was occurring affected prescribing.

The length of studies varied considerably. Some were of two weeks duration[20, 125], some four weeks[44, 49, 124], 30 days[64], 5 weeks[24, 53], two months/ eight weeks[25, 56, 66], 10 weeks[1], 12 weeks[63], 13 weeks[22, 23, 43], four months[45, 51], six months, eight months[50], 10 months[48, 69], one year[61], two years[4], three years[68] and four years[65]. The number of patients included in studies also varied considerably from 34[11] to 355409,[61] although one study did not provide information on the number of patients included in the study.[49]

The frequency of off-label and unlicensed prescribing for children was reported for various settings including various intensive care units (NICU,

paediatric ICU), surgical or medical wards, general paediatric medical wards, respiratory and cardiology wards, oncology wards, gastroenterology outpatient departments, Emergency Departments and others. Some studies focused on patients in specific age groups (e.g. neonates) or with specific conditions such as oncology, paediatric pain management or adverse drug reactions associated with off-label and unlicensed drug use.

The age of patients included in the studies varied, with some studies including only neonates[1, 11, 43, 45], others including children aged up to 11 years[62], up to 13 years[25], less than or up to 14 years[55, 63], less than 15 years[51], less than or up to 16 years[48, 59], less than or up to 17 years[47, 65], up to 18 years[4, 23, 56, 64], less than 19 years[67] and less than or up to 20 years[22, 57]. In several studies, the youngest child was one month old or one year old.[63, 66] [59] In studies conducted exclusively in neonates the extent of off-label and unlicensed prescribing reported has been higher than in some other hospital settings so by not including children under one month or one year of age, this may impact considerably on the actual extent of off-label or unlicensed prescribing.

Several different age classifications were used by researchers and these varied considerably. Examples of age classification included those used by 'tJong et al.[54] (0 to < 1 month, 1 to < 6 months, 6 months to < 2 years, 2 to < 6 years, 6 to < 12 years, 12 years and older), Shah et al.[61] (≤ 28 days, 29 days to one year, 2 - 5 years, 6 - 12 years, 13 - 17 years), Bazzano et al.[68] (infant < 1 year, toddler 1 to < 2 years, preschool 2 to < 6 years, school age 6 to < 12 years, adolescent 12 to < 18 years), Palcevski et al.[57] [neonates (0-28 days), infants (29 days - 1 yr), toddlers (1-2 yrs), preschool children (3-6 yrs), school children (7-11 yrs), adolescents (12-19yrs), McKinzie et al.[64] (zero to 2 years, three to 1 years, 12 to 17 years) and Ruiz-Antoran et al.[48] (infants younger than two years, children between two and 10 years, adolescents 11 years and older). However, a number of researchers used the European Medicines Agency (EMA)[6] age classification including Hsien et al. and others[42, 50, 55, 69] (term newborn infants/ neonates aged zero to 27 days, infants and toddlers aged 28 days to 23 months, children aged two to

11 years, adolescents aged 12 to 18 years) so this internationally accepted classification was adopted for the current study.

5.10.1 Exclusions

Possible selection bias may have resulted from the exclusion of certain patients and drugs. For example, McKinzie et al.[64] excluded paediatric patients who presented exclusively for psychiatric evaluation. The exclusion criteria of drugs varied with studies. Several studies excluded standard IV replacement solutions, blood products, oxygen therapy and flushes of sodium chloride 0.9% or heparin used to maintain patency of intravenous lines[22, 24, 124] whereas others excluded over-the-counter drugs or unscheduled medications[62, 64], immunisations/ vaccinations[62, 64] total parenteral nutrition (TPN)[53, 54, 56, 62], eye drops, ear drops, nasal preparations, gargles and topical creams[56]. Other studies included all prescription and non-prescription medications in the evaluation. [60]

In some studies, patients who did not receive any medications were excluded from the study.[56] By including only patients prescribed medications, the percentage of patients prescribed off-label or unlicensed drugs would be higher than if all patients, including those that did not receive medications, were included.

In the current study, the exclusion criteria included oxygen therapy, standard intravenous (IV) replacement solutions, blood products, flushes of NaCl 0.9% or heparin used to maintain patency of IV lines and total parenteral nutrition (TPN). Most of these are not directly related to drug treatment and their omission was based on them not being directly used as drug therapy. Some would have influenced the number of unlicensed items prescribed. Procedures that did not involve the administration of agents for therapeutic effect, such as flushes to maintain patency of IV lines would also not have influenced the extent of off-label or unlicensed prescribing. Although TPN is not an active drug treatment, if it had been included in the study, it would have been classified as an unlicensed product. It is noteworthy that drugs

can be added to TPN and as this would have been recorded on the medication chart, such drugs would have been included in the current study.

In considering the different exclusion criteria in various studies and the differences in reporting, a set of standard exclusions should be devised to allow accurate comparisons to be made between studies. It would be useful if the standardised parameters were set by the WHO as part of its role as a leader in global health matters and shaping the health research agenda, including setting norms and standards.

5.10.2 Variations in off-label and unlicensed definitions

Considerable variation in the extent of off-label and unlicensed prescribing is reported from different studies. This may be explained in part by the various definitions that have been used to describe off-label and unlicensed drugs. Thus the results are not directly comparable but provide an overall view of the issue. For example, some studies considered only one type of off-label use, such as McKinzie et al.[64] who conducted a study in the Emergency Department in which off-label drug use was based solely on age-specific prescribing guidelines without considering indication, route of administration or dosage. In a study in the US outpatient setting, Bazzano et al.[68] used only age and indication to determine off-label status whereas Lass et al.[67] defined off-label as lack of paediatric information or contraindication to the use of the drug as well as age. Bajcetic et al.[4] defined off-label drug use with respect to age, dose and route of administration but not indication.

Many studies adopted the definition for off-label prescribing outlined by Turner et al. [22, 23] which describes off-label use as the use of drugs outside the manufacturer's approved license with regard to age, dose, route of administration and different indication or contraindication.[25, 43, 46, 47, 50, 54, 66]. Some researchers included a separate off-label category for drugs with no information for paediatric use [11, 55, 56, 69] while other researchers [42] classified drugs with no paediatric information as off-label for age. Some researchers considered up to eight types of off-label categories including lack of

paediatric information, age, lower than licensed dose, higher than licensed dose, indication, route of administration, less frequent than licensed frequency and more frequent than licensed frequency.[56]

The definitions of unlicensed drugs also varied. Turner et al. defined unlicensed drugs as follows: modification to licensed drugs (e.g. crushing tablets to produce a suspension), licensed medicines in a modified formulation manufactured under a special manufacturing license (e.g. when an adult formulation is not suitable for use in children and a smaller dose must be formulated), new medicines under a special manufacturing license (e.g. caffeine injections for apnoea of prematurity), medicines used before a license has been granted, imported medicines or chemicals used as medicines.[22] Several researchers used this classification system.[47, 50] However, other researchers defined unlicensed drugs as "modified" or "home label" preparations [53] without any further classifications. Lee et al.[56] classified unlicensed drugs as extemporaneous preparations or unregistered products. Palcevski et al. classified drugs not approved for use in Croatia or those approved for use in Croatia but not for use in children, as unlicensed.[57] These researchers classified off-label drugs as drugs approved for use in children but for other indications or routes or age groups.[57] Gavrilov et al. defined unlicensed use only as modification of a licensed drug.[66] Lass et al defined unlicensed as a drug with no official marketing authorisation in Estonia.[67] Bajcetic et al. classified unlicensed as an unapproved formulations (e.g. crushing tablets to make a syrup).[4] 'tJong et al. defined unlicensed drugs as drugs that were manufactured or modified by the hospital pharmacy, those that had an information text without dosage guidelines in children and drugs that were contraindicated for use in children.[54]

A different definition was used by Santos et al. who defined unlicensed drugs as extemporaneous preparations that were a) manufactured (home-label medications) or b) modified by the hospital or nurse. These researchers also classified drugs as unlicensed if the safety and efficacy in the paediatric population were not established or if the drug was contraindicated for use in children. Where there was a discrepancy with the license information for age

(or weight), dose (or frequency), route of administration or formulation, these drugs were classified as off-label medicines.[59] These researchers reported that the most frequent reason for unlicensed medications was that "safety and efficacy have not been established in children".

Many researchers assigned more than one classification for off-label drugs and classified some drugs as off-label for multiple reasons. However, Hsien et al.[42] stated that an off-label drug cannot be classified in more than one classification.[42] The different definitions of off-label and unlicensed medicines used by various researchers' categorisation make comparisons between studies difficult or impossible. A standardised definition of "off-label" and "unlicensed" should be adopted internationally and could perhaps be initiated by the WHO.

Most studies reported both off-label and unlicensed prescribing [1, 4, 11, 20, 22, 24, 25, 43, 46, 47, 49-51, 53, 54, 56, 57, 59, 66, 124] with a few reporting only on off-label prescribing.[42, 56, 60-65, 67-69] Reporting of off-label prescribing in patients varied with different studies. For example, by excluding patients that were not prescribed medicines [56] a higher percentage of off-label prescribing in patients is likely to be reported. Some studies included patients that did not receive medicines but when they reported the percentage of patients that received off-label medicines, they only considered patients that were prescribed medicines. For example, in a recent study in Spain involving 695 children, 207 received medicines of which 47.3% received off-label medicines.[48] If the number of patients receiving off-label drugs was reported in relation to all patients in the study (i.e. 695 children) the percentage would be much less (i.e. 14.1% i.e. 98 / 695).

Similar reported data occurred in a study in Croatia which involved 691 paediatric patients.[57] Of these, 531 received drugs, and of these, 254 received either off-label or unlicensed drugs. The researchers reported the percentage of patients receiving off-label or unlicensed drugs as 47.8% (i.e. 254/531) but if the percentage had been reported as a percentage of the total study population, then 36.8% (i.e. 254/691) of patients would have been

reported as receiving an off-label or unlicensed drug which would have been closer to the findings reported in the current study. By contrast, in a recent Portuguese study involving 700 children of whom 427 were prescribed drugs of which 197 were prescribed off-label drugs, researchers reported that 28.1% of all children received one off-label prescription. These researchers reported the finding based on the whole study population.[69]

In the current study, 378 patients out of 1037 patients were prescribed off-label or unlicensed drugs and 338 patients did not receive any drugs. The percentage of patients receiving off-label or unlicensed drugs in this study was reported as 36.5% in relation to all patients. However, if patients not prescribed drugs were excluded, the percentage of patients prescribed off-label or unlicensed drugs would be 54.0% (i.e. 378 / 699). Therefore reported percentages can be manipulated depending on how the findings are reported.

The percentage of patients reported as receiving off-label or unlicensed drugs in the current study, which was calculated as 36.5% by considering the whole study population, was similar to those reported by studies in the UK, Israel and Ireland.[22, 25, 66] However, it is difficult to make direct comparisons between studies as the UK and Ireland studies were inpatient studies and the study in Israel was an outpatient study. Further, the age of patients included in the studies was different with the UK study including patients less than 20 years, the Ireland study including patients less than 13 years and the Israel study including patients from one month to 18 years.

5.11 What is happening overseas

Since 1997, legislation was introduced in the United States, including the Paediatric Rule Regulation 1998, Best Pharmaceutical for Children Act (BPCA) 2002 and the Paediatric Research Equity Act (PREA) 2003, to ensure that high quality safe and effective drugs, that were ethically researched, were approved and made available for use in children.[126, 127] For

drugs where paediatric studies are required, the PREA requires pharmaceutical companies to conduct paediatric studies in the same drug that is approved for adults use.[126] The BPCA provides an incentive for pharmaceutical companies to conduct paediatric studies requested by the FDA by providing an additional six months of marketing exclusivity.[127] Prior to BPCA and PREA becoming law, more than 80% of drugs approved for use in adults were being use off-label in children despite a lack of safety and efficacy data. Since the introduction of the new legislation, the number of adult drugs used in children without adequate safety and efficacy data has decreased to 50% during the past 15 years.[85, 106]

Following the experience in the US, the Paediatric Regulation was implemented by the European Union in January 2007. This established a framework of requirements, incentives, obligations and rewards for pharmaceutical companies similar to the PREA in the United States. The central instrument of the Paediatric Regulation is the Paediatric Investigation Plan (PIP) which aims to obtain relevant data through clinical trials without subjecting children to unnecessary trials. PIPs are approved by the Paediatric Committee (PDCO) established within the EMA and all pharmaceutical companies are required to submit a PIP when a new drug is marketed (unless a waiver has been granted).[128] Reflecting on the successes of the Paediatric Regulation after five years since its implementation in 2007, the EMA recently reported that more high quality research in paediatric medicines was taking place, better information on the use of medicines in children had become available (221 changes about safety and efficacy, from submission of old or new studies and 89 additions to dosing information for children as a result of PIPs) and there were more medicines for children with age appropriate dosage forms.[129]

On the world front, in 2007 the WHO launched the "Make medicines child size" campaign and established the Model List of Essential Medicines for Children, which is now in its fourth version.[90, 91] Further, the EMA and the FDA in the United States have agreed on principles to interact and exchange information on paediatric matters, to foster the global development of

medicines for children. Collaboration with other regulators outside the European Union and with the WHO are also ongoing.[130]

5.12 What is happening in Australia

Since the mid-1990s, initiatives addressing issues related to paediatric medicines have been proposed through professional and government bodies, including paediatric medicines research to ensure quality use of medicines (QUM) which is part of the National Medicines Policy.[85] Despite some recent initiatives such as the availability of an evidence based and peer reviewed paediatric prescribing information resource, guidelines for off-label prescribing published in the Medical Journal of Australia and the ongoing work of the Paediatric Medicines Advisory Group (PMAG), there is still a lack of any legislative and regulatory reforms addressing paediatric medicines in Australia.[77, 94, 99]

Both the current Western Australian study and the recent Tasmanian study reported that a high percentage of patients receive off-label drugs and that many medicines are used in an off-label manner because of the lack of appropriate safety and efficacy data.[62] In addition it is evident that many medicines have been used off-label for decades. The initiatives by the US and Europe show a strong commitment by governments and society as a whole to stimulate development and study of drugs used in paediatrics and provide important scientific data for improvement of paediatric therapy but there is currently no specific government commitment in Australia to give high priority to paediatric medicines issues.

5.13 Patient related issues

5.13.1 Informed consent

In the current study, no documentation was found in any of the paediatric medical records documenting parent or carer's informed consent when off-label or unlicensed drugs were prescribed to a patient. As the study was retrospective, it was not possible to verify if an oral parent or carer's informed consent was obtained and there was no evidence of this in the medical records. Other researchers have also reported a lack of informed consent documents.[48, 62]

The benefits and risks associated with off-label or unlicensed prescribed drugs should be discussed with parents or carers and consent obtained, preferably with documentation of a signed consent form, especially when high quality evidence for use of a medicine is lacking. Further, Ballard et al. suggest that in the latter case, approval of a hospital drug committee should be obtained.[62]

5.13.2 Patient safety and ethical issues

Since the study conducted by Turner at PMH in 1999,[24] the current study suggests that the percentage of inpatients prescribed off-label and unlicensed drugs has increased, especially patients prescribed off-label drugs. The individual percentages of off-label or unlicensed drugs cannot be compared as only a combined value of 16% off-label and unlicensed drugs were reported in Turner's study. However, the percentage reported in the current study is higher suggesting that the rate of prescriptions for off-label and unlicensed use has increased in the last decade.

Other comparative studies have also reported an increase in the rate of off-label prescribing, especially in newborns. In a recent study in Finland researchers compared prescribing trends between 2001 and 2011. They

reported that despite the implementation of the European Paediatric Regulation in 2007, the number of patients prescribed at least one off-label or unauthorised (unlicensed) drug had increased from 58% in 2001 to 79% in 2011.[125] However, they added that the four year period that the regulation had been in force might be too short for significant changes.[125]

One of the assumed consequences of off-label and unlicensed prescribing is the potential for an ADR. A ten year study in Denmark that analysed spontaneous reporting of ADRs in children aged zero to 17 years reported that 17% of ADRs were associated with off-label use and that 60% of these were severe.[74] In another study, researchers reported that ADRs related to off-label use was lower than the rate for drugs with approved (licensed) uses.[131] Although these findings are conflicting, in a recent 12 month prospective study of ADRs involving 6020 children admitted to a paediatric hospital in the UK, researchers reported that off-label and unlicensed medicines were more likely to be implicated in an ADR than authorised medicines (relative risk 1.67, 95% CI 1.38, 2.02, $p < 0.001$).[132] This was due to the fact that many of the ADRs related to off-label and unlicensed use of drugs in oncology patients.

In the current study, reporting of ADRs related to off-label or unlicensed drug use was not well recorded in patient medication records. This made it impossible to determine whether the level of ADRs was greater with off-label and unlicensed drugs compared to licensed drugs. Whether the lack of reporting was due to litigation fears or just simple omissions was not able to be determined. Although off-label and unlicensed prescribing is not illegal, it has been reported previously that physicians and hospitals can be wary of using medicines in this way for fear of litigation.[133] If ADRs were suspected of being a major factor associated with off-label and unlicensed prescribing at PMH, a study should be conducted collecting data prospectively. The only concern would be as to whether the same level of off-label and unlicensed prescribing would be maintained once awareness of the study emerged and could influence the reporting of ADRs as these may require verbal enquiry.

In Australia, ADRs can be reported either online or via the "Blue Card" and this probably involves mainly licensed (or on-label) drug use. ADRs associated with off-label and unlicensed drugs are likely to be underreported, not only in the current study but also other studies.[48] Therefore monitoring, pharmacovigilance and documentation of ADRs associated with off-label and unlicensed drug use should be improved.

Drugs are registered to demonstrate efficacy, safety and toxicity including ADRs to ensure that when a drug is prescribed to a patient that the patient is likely to benefit from the drug and not have untoward effects above an acceptable level. The use of off-label and unlicensed drugs raises some important ethical issues as to whether the drug used in an unapproved manner should be considered as an experimental use that warrants patient or parent consent prior to administration.

With respect to off-label drugs, neither the benefit nor the risk has been demonstrated either for that indication, dose or in that age group. However, by allowing off-label prescribing, it gets around the need for a sponsor to demonstrate efficacy in those categories. For unlicensed drugs there is no information for the general population but for one person it may be acceptable. The availability of unlicensed drugs for one person provides access to an individual who would like access to the product but does not expose the community to the risk. But since off-label prescribing is so highly prevalent, the community is exposed to the risk, especially children.

Recently, in a meeting of experts that included experts in drug development and formulation, neonatal intensive care, paediatric clinical pharmacology and others, more than 80% advised that poor formulation of a drug was occasionally associated with an untoward effect such as prolonged hospitalisation or cause of a new condition. Further, nearly 40% believed that lack of a properly formulated parenteral drug occasionally contributed to death.[134] Hence the underlying ethical issues are whether off-label drugs and unlicensed drugs should be permitted and the level of risk in its acceptance.

In addition, if it was not permitted there would be an issue as to whether sponsors would carry out studies in children as they are a small market.

In Australia, as a result of the support of the Australian Health Ministers' Advisory Council (as part of the Paediatric Pharmaceuticals Resource project) the AMH Children's Dosing Companion was recently introduced.[99] This publication was prepared from the best available evidence to support the recommendations and is a welcome resource for professionals who devote their efforts to provide high quality care for children. For example, although the approved license for midazolam is for the injection solution to be administered IV or IM, the AMH Children's Dosing Companion provides doses for oral, buccal and intranasal administration, all of which are off-label for route of administration. Under the heading "Off-label use" it states that the PI does not include doses for seizures, or for oral, buccal or intranasal use. It does not provide further information to justify off-label use by different routes of administration to those in the accepted license. This is similar for other drugs that are also used off-label such as clonidine for which the approved license does not include preoperative sedation and analgesia. However, the AMH Children's Dosing Companion provides doses for children aged one to 18 years.[99]

Considering that the prevalence of off-label and unlicensed prescribing in this study was almost one third of all patients and given that the prevalence of off-label and unlicensed prescribing in other countries has also been reported to be high, especially in some settings (e.g. inpatients) and some patient age groups (e.g. neonates), governments around the world need to be aware of a potential public health hazard. A government sponsored group of experts, perhaps even the WHO, should consolidate and evaluate the quality of evidence for the prescribing of drugs for children. This could be achieved through systematic reviews including meta-analyses, to identify whether there is sufficient evidence for the off-label or unlicensed prescribing including the dose and range of age groups of children where pharmacokinetics could have an impact. Where notable deficiencies are

reported, studies should be sponsored to provide an adequate evidence-base for their prescribing.

5.14 Lincomycin

In Australia, the use of parenteral lincomycin in hospitals, including ICUs, exceeds parenteral clindamycin usage.[135] This preference of lincomycin over clindamycin may have been partly due to the lower acquisition cost of lincomycin, although there have been recent changes in the cost of these agents, so they now both cost the same. This may have an impact on future prescribing trends. However, lincomycin is currently the only injectable lincosamide available on the PBS.[136] Further, the Australian Therapeutic Guidelines (Antibiotics) presents both drugs as equivalent treatments for serious infections resulting from *Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus agalactiae*. [123]

Lincocin® (which contains lincomycin hydrochloride) can be administered by direct intramuscular injection every 12 to 24 hours at a dose of 10 mg/kg/day of lincomycin. Alternatively, intravenous doses can be administered on the basis of one gram Lincocin® (lincomycin as the hydrochloride) diluted in not less than 100 mL of appropriate IV solution and infused over at least one hour.[30] Lincocin® is commonly used in an unlicensed manner by adding the drug to various IV solutions including sodium lactate, 0.9% sodium chloride, 5% glucose and 10% glucose solutions. Current stability information on lincomycin in these IV solutions is limited to the compatibility of lincomycin in these IV fluids which are physical determinations rather than chemical determinations.[30] Physical compatibility has been reported only for 24 hours at room temperature.[101] However, the expiry dates for many stable compounds can be extended when prepared aseptically thus potentially reducing wastage. Further, more patients are being treated at home so less home visits to obtain additional doses from an attending nurse may increase convenience.

This study investigated the stability of Lincocin® in sodium lactate (Hartmann's), 0.9% sodium chloride, 5% glucose and 10% glucose solutions over 31 days. An initial investigation was carried out to ensure that the Lincocin® sample met the BP 2013 specifications for the content of lincomycin in the lincomycin injection, which should be 92.5 to 107.5% of the stated amount.[36] The amount of lincomycin base in a 0.6 mg/mL lincomycin hydrochloride sample prepared from Lincocin® was found to contain 0.629 mg/mL lincomycin, equivalent to 104.9% of the stated amount. Hence the calculated quantity of lincomycin in Lincocin® injections (104.9%) met the specifications of the BP.

Stability studies testing the degradation of 0.6 mg/mL lincomycin in 0.1 M hydrochloric acid solution, 0.1 M sodium hydroxide solution and 3% hydrogen peroxide solution at 60°C showed that lincomycin degradation occurred most rapidly in hydrogen peroxide suggesting that lincomycin hydrochloride readily undergoes oxidation. Less rapid degradation was observed in acid solution with 48.8% lincomycin hydrochloride remaining in acid solution after seven days compared to 8.0% remaining in base solution after the same time. In a study investigating the stability of 0.4% lincomycin hydrochloride in 0.1 N hydrochloric acid solution at 37°C and 70°C, it was reported that lincomycin showed no degradation for at least 48 hours at 37° C and degraded slowly (half-life 39 hours) at 70°C.[106]

The stability of lincomycin was tested over four weeks at 25°C in the four different IV solutions stated above (sodium lactate (Hartmann's Solution), 0.9% sodium chloride solution, 5% glucose solution and 10% glucose solution). Lincomycin was very stable in all four IV solutions and showed very little degradation over time. All samples had a shelf-life of 744 hours or 31 days at 25°C. In a study investigating the stability of clindamycin in 5% dextrose and 0.9% sodium chloride at 4°C and at room temperature (23°C) over 21 days, researchers reported that the degradation of clindamycin was slow with less than 5% loss occurring at various concentrations of clindamycin in each diluent and at each temperature. This is similar to

findings on lincomycin in the current study although a single concentration (0.6 mg/mL) was used in each IV solution.[137]

The degradation of lincomycin hydrochloride at 80°C at pH 2.00, 3.00, 4.00, 6.10 and 8.00 was also investigated. The rate constant was lowest at pH 4.00. The results showed that lincomycin had the greatest stability at pH 4.00, with a calculated shelf-life of 4.59 days. It was least stable at pH 2.00, with a calculated shelf-life of 0.38 hours.

Lincomycin hydrochloride (Lincocin®) is only available as a 2 mL ampoule. When lincomycin hydrochloride is required in an appropriate IV solution, this necessitates that the required amount is transferred into the IV infusion via a syringe. Aseptic technique is essential for this and usually requires a hospital pharmacy environment. Once prepared, however, the solution could be used outside the hospital environment.

5.15 Study limitations

There were several limitations to this study. There were few neonates included in this study as they are usually treated at another hospital unless they require treatment after discharge. There was a smaller percentage of inpatients (24.5%) in this study than outpatients (36.6%) or Emergency Department patients (38.9%). However, for some outpatients, all of their prescribing related to their admission in 2008 as an inpatient. For these patients, their prescribing details were recorded and they were classified as an inpatient for the study. The transfer from outpatient to inpatient may have decreased the level of prescribing attributed to the outpatient category.

Some medical records were not available as patients had either been readmitted to the hospital so their medical chart was in use on the ward or they had recently been discharged so their medication chart was still waiting to be filed. It was expected that more patients prescribed psychotherapeutic drugs would have been identified but it could be that their medical records

were amongst those difficult to obtain which could have occurred for child protection cases or where they were being used on the ward. The study however accessed medical records at least 86.5% of the time after the end of 2008.

There were limitations with the hierarchical classification system because in a number of cases, if a hierarchical approach had not been used, drugs could have been classified into a number of categories. The classification system may have lowered the number of unlicensed drugs reported. In some categories there were low levels of unlicensed prescribing and hence an even larger sample would be necessary to ensure adequate power in that subgroup to make comparisons. The hierarchical system used classifies medicines as off-label or unlicensed with the same frequency as recording all possible reasons, however the number of reasons for which an item could have been classified would be lower in this study.

5.16 Conclusion

This study provides the first data on the prevalence of off-label and unlicensed prescribing from a random sample of patients from a major paediatric hospital which gave an overall off-label and unlicensed prevalence of 28.3%, of which 25.7% accounted for off-label prescribing and 2.6% accounted for unlicensed prescribing. The percentage of patients prescribed at least one off-label or unlicensed drug was 36.5% with the highest percentage of off-label prescribing associated with nervous system drugs and the highest percentage of unlicensed prescribing with systemic hormonal preparations excluding sex hormones. Most drugs were used in an off-label manner rather than in an unlicensed manner. The ten most commonly prescribed off-label drugs were ondansetron, Painstop Day®, salbutamol, oxycodone, paracetamol, midazolam, fentanyl, ticarcillin/ clavulanic acid, amoxicillin and flucloxacillin. The most commonly prescribed unlicensed drugs were dexamethasone and dilacaine.

Of the inpatients that were prescribed drugs, 78% were prescribed off-label drugs. Further, children aged between two and 11 years were prescribed the highest percentage of off-label drugs (85%). The highest percentage of unlicensed drugs were prescribed to outpatient infants aged 28 days to 23 months (17%).

These findings indicate that almost one-third of patients are being exposed to medicines for indications that are unregistered and/or doses that are unregistered. This situation is a potential public health hazard especially for inpatients and children aged two to eleven years since off-label prescribing was found to be highest in these groups. Children are considered a vulnerable group of patients and governments around the world need to be made aware of a potential public health disaster from the current system.

As a first step, a government sponsored group of experts should consolidate and evaluate the quality of evidence for the prescribing of drugs in paediatric populations. Where there are notable deficiencies then studies should be sponsored to provide an adequate evidence-base for their prescribing.

5.17 Recommendations

- To allow international studies to be comparable, guidelines should be provided outlining an optimum study design including clear definitions of the terms off-label and unlicensed and age groups. The definitions provided by Turner et al. have been used by a number of researchers as they are comprehensive and unambiguous. It is recommended that a major organisation, such as the WHO, provide a universal definition of the terms off-label and unlicensed prescribing and propose international study guidelines to provide better consistency so data can be comparable.
- A system for monitoring off-label and unlicensed prescribing in children across Australia is recommended.
- All off-label and unlicensed prescribing should require a mandatory consent form. This may increase awareness among health professionals that they are prescribing a drug in an off-label or unlicensed manner and would ensure that parents/ carers were appropriately informed.
- The current study describes the findings of off-label and unlicensed prescribing in the major children's hospital in WA. A major study at a national level involving several major paediatric hospitals in Australia would be valuable to determine the robustness of the findings in the current study.
- A committee to establish evidence based paediatric data from published studies should be established, possibly at the level of the WHO, so that vital information on safety and efficacy of drugs could be available and accessible for all health practitioners in the world for the benefit of children.
- It is proposed to publish the lincomycin hydrochloride stability data in a well regarded journal so that this information is widely available to the pharmacy community. In the current climate of off-label and unlicensed products, this seems to be the only option available.

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Appendices

Appendix 1 - Summary of studies reporting off-label and unlicensed drugs prescriptions.

Country	Study	Study type	Length of study	Type of patients or study wards	Number of patients	Age of patients	Total prescriptions/ prescription episodes	Percentage prescriptions off-label (OL)	Percentage prescriptions unlicensed (UL)	Percentage prescriptions OL or UL	Patients receiving OL or UL drugs
UK	Turner S et al. [51]	P	4 months	Paediatric intensive care unit	166	1 day - 15 yrs	862	Not reported	Not reported	31%	70%
US	McKinzie et al. [64]	R	30 days	Emergency Department patient charts	359	4 days - 17 years	Not reported	Not reported	Not reported	Not reported	43 % OL
UK	Turner et al. [22]	P	13 weeks	Medical & surgical paediatric wards	609	4 days - 20 years	2013	18%	7%	25%	36%
UK	Conroy et al. [43]	P	13 weeks	Neonatal intensive care unit	70	neonates	455	55%	10%	65%	90%
UK	Turner et al. [23]	P	13 weeks	5 different wards e.g. surgical, medical, neonatal surgical	1046	1 day - 18 yrs	4455	Not reported	Not reported	35%	48%
Australia	Turner et al. [24]	P	5 weeks	Medical ward & surgical ward (100 patients from each)	200	49 days - 18 years	735	Not reported	Not reported	16%	36%
Across Europe	Conroy et al. [58]	P	4 weeks	General paediatric medical wards in 5 hospitals	624	4 days - 16 years	2262	39%	7%	46%	67%
France	Avenel et al. [44]	P	4 weeks	Neonatal intensive care unit	40	Neonates	257	63%	10%	73%	Not reported
Israel	Gavrilov et al. [66]	R	2 months	Outpatients in the General Paediatric Ambulatory Unit	132	1 month - 18 years	222	26%	8%	34%	42%
UK	Conroy et al. [49]	P	4 weeks	Children's hospital acute medical & acute surgical ward	not provided	Not reported	715	33%	0%	33%	Not reported

Country	Study	Study type	Length of study	Type of patients or study wards	Number of patients	Age of patients	Total prescriptions/ prescription episodes	Percentage prescriptions off-label (OL)	Percentage prescriptions unlicensed (UL)	Percentage prescriptions OL or UL	Patients receiving OL or UL drugs
Ireland	Craig et al. [25]	P	2 months	Paediatric medical ward	74	1 week - 13 years	237	19%	3%	22.00%	43%
Netherlands	t Jong et al. [53]	P	5 weeks	3 ICUs and one medium care unit	237	0 days - 17 years	2139	18%	48%	66%	90%
Israel	Barr et al. [45]	P	4 months	Neonatal intensive care unit	105	Neonates	525	59%	16%	75%	93% off label
Australia	O'Donnell et al. [1]	P	10 weeks	Neonatal intensive care unit	97	Infants	1442	47%	11%	58%	80%
Italy	Pandolfini et al. [63]	P	12 weeks	Paediatric wards from 9 participating Italian hospitals	1461	1 month - 14 years	4265	60%	0.2%	60.2%	82%
Netherlands	t Jong et al. [54]	P	5 months	Paediatric ward & neonatology unit	293	0 days to 16.7 years	1017	44%	28%	72%	92%
UK	Conroy et al. [46]	P	4 weeks	Oncology inpatients and outpatients	51	0.6 - 16.3 years	569	26%	19%	45%	100%
UK	Dick et al. [47]	R	6 months	Paediatric gastroenterology outpatient department	308	20 days - 17 years	777	37%	12%	49%	Not reported
Germany	Neubert et al. [50]	P	8 months.	Paediatric isolation ward	178	5 days - 17 years	740	26.4%	0.4%	26.8%	52%
Belgrade	Bajcetic et al. [4]	P	2 years	Paediatric cardiology ward	544	4 hours - 18 years	2037	47%	11%	58%	76%
Switzerland	DiPaolo et al. [55]	P	6 months	Various wards e.g. neonatal, paediatric, intensive care	60	3 days - 14 years	483	25%	24%	49%	100%

Country	Study	Study type	Length of study	Type of patients or study wards	Number of patients	Age of patients	Total prescriptions/ prescription episodes	Percentage prescriptions off-label (OL)	Percentage prescriptions unlicensed (UL)	Percentage prescriptions OL or UL	Patients receiving OL or UL drugs
US	Eiland & Knight [60]	P	6 months	Clinic, the emergency dept or the paediatric ICU	403	3 days - 18 years	1383	31%	Not reported	Not reported	Not reported
Italy	Dell'Aera et al. [11]	P	2 months	Neonatology intensive care unit	34	neonates	176	51%	12%	63%	51%
US	Shah et al. [61]	R	1 year	31 tertiary care paediatric hospitals	355409	≤ 18 years	Not provided	Not reported	Not reported	Not reported	78.7% OL
Brazil	Santos et al. [59]	P	5 months	Ward with several different paediatric specialities	272	1 - 16 years	1450	39.6%	5.5%	45.1%	83%
Germany	Hsien et al. [42]	P	6 months	Pneumology & cardiology ward	417	1 day - 40 years	1812	31%	Not reported	Not reported	61% OL
US	Bazzano et al. [68]	R	3 years	National Ambulatory Medical Care Surveys data	7901 OP visits	0 - 17 years	312 million visits	62%	Not reported	Not reported	59% OL
Finland	Lindell-Osuagwu et al. [20]	P	2 weeks	NICU, general and surgical ward	141	< 18 years	629	36 %	13 %	49 %	76 %
Estonia	Lass et al. [67]	R	1 year	Outpatients	151476	< 19 years	467334	31%	0.1%	31.1%	Not reported
Italy	Zanon et al. [65]	R	4 years	8 pediatric emergency departments	19879	0 - 17 years	19879 doses of antiemetic	30%	Not reported	Not reported	Not reported
Croatia	Palcevski et al. [57]	P	12 months	Hospitalised children in the Department of paediatrics	691	1 day - 20 years	1643	12%	13.3%	25%	48%
Portugal	Ribeiro et al. [69]	R	10 months	Paediatric emergency unit	700	4 days - 18 years	724	32.2%	Not reported	Not reported	28.1% OL
Spain	Ruiz-Antoran	R	10 months	Pediatric gastroenterology outpatient clinic	695	22 days - 15.6 yrs	331	33.2%	Not reported	Not reported	47%

Country	Study	Study type	Length of study	Type of patients or study wards	Number of patients	Age of patients	Total prescriptions/ prescription episodes	Percentage prescriptions off-label (OL)	Percentage prescriptions unlicensed (UL)	Percentage prescriptions OL or UL	Patients receiving OL or UL drugs
	et al. [48]										
Australia	Ballard et al [62]	R	4 months	General paediatric ward	300	1 day - 11 years	887	32%	Not reported	Not reported	57% OL
Malaysia	Lee et al [56]	P	8 weeks	3 Intensive care units	194	1 day - 16 years	1295	34.1	27.3	61.4%	92.4%

Appendix 2 - Ethics approval PMH

Re: CARTIN / Bruce Sutherland / Peter Czarniak

Government of **Western Australia**
Department of **Health**

Child and Adolescent Health Service

PMH 100 CENTENARY 1909-2009

Mr Lewis Bint
Pharmacy
Princess Margaret Hospital for Children
Roberts Road
SUBIACO WA 6008

Dear Mr Bint

Audit 103QP – Prescription of off-label or un-registered medications (GEKO 1944)

This letter confirms that the above audit has been reviewed and approved by the relevant Hospital Quality Improvement Committee and approved by Executive Director of Medical Services in accordance with the National Statement 2007 (clauses 5.1.18 to 5.1.23).

The Executive Director has recommended this audit be noted by the Ethics Committee and requested a number for the purpose of publication.

Yours sincerely,

Marlene Clayton
Ethics Committee Secretary

3 December 2009

Princess Margaret Hospital for Children
Roberts Road Subiaco WA 6008
GPO Box D184 Perth WA 6840
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Appendix 3 - Ethics approval Curtin University

Curtin University

Memorandum

To	Petra Czarniak, School of Pharmacy
From	A/Prof Stephan Millett, Chair, Human Research Ethics Committee
Subject	Protocol Approval **PH-13-11**
Date	14 September 2011
Copy	Professor Jeff Hughes, School of Pharmacy

Office of Research and Development

Human Research Ethics Committee

Telephone 9266 2784
Facsimile 9266 3793
Email hrec@curtin.edu.au

Thank you for your "Form C Application for Approval of Research with Low Risk (Ethical Requirements)" for the project titled *"Issues with the Use of Medicines in paediatrics: Off;label and Unlicensed Use, and Pharmacokinetic Uncertainty".* The Committee notes the prior approval by Princess Margaret Hospital Ethics Committee (Ref: Audit 103QP, 3 December 2009) and has reviewed your application consistent with Chapter 5.3 of the *National Statement on Ethical Conduct in Human Research.*

Please Note: The audit component of Phase 1 is approved. Subsequent phases of the project are subject to a separate view via Form A Application.

Approval of this project is for a period of twelve months **14-09-11** to **14-09-12**.

The approval number for your project is **PH-13-11**. *Please quote this number in any future correspondence*. If at any time during the twelve months changes/amendments occur, or if a serious or unexpected adverse event occurs, please advise me immediately.

Yours sincerely,

Associate Professor Stephan Millett
Chair Human Research Ethics Committee

Please Note: The following standard statement must be included in the information sheet to participants:
This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number PH-13-11). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or hrec@curtin.edu.au

CRICOS Provider Code 00301J

Appendix 4 - List of all 330 prescribed drugs (licensed, off-label and unlicensed) included in the study and their frequencies

Drug Name	Frequency	Drug Name	Frequency
Acetylcysteine	3	Azathioprine	4
Aciclovir	7	Azithromycin	9
Actrapid	6	Baclofen	1
Adrenaline	11	Benzathine penicillin	1
Albey bee venom	2	Benzocaine/ phenazone	2
Alfentanil	2	Benzylpenicillin	9
Allopurinol	1	Betamethasone	11
Alpha-keri	1	Betaxolol	1
Alprostadil	1	Bisacodyl	2
Alteplase	2	Botulinum toxin	5
Aminophylline	1	Brimonidine	1
Amitriptyline	3	Brimonidine/ timolol	1
Amlodipine	1	Brinzolamide	1
Amoxicillin	59	Budesonide/ eformoterol	2
Amphotericin B	1	Bupivacaine	1
Aprepitant	3	Buscopan	1
Aspart insulin	22	Calamine	1
Aspirin	7	Calcitriol	1
Atenolol	2	Calcium carbonate	4
Atomoxetine	1	Calcium folinate	1
Atorvastatin	1	Captopril	1
Atovaquone/ proguanil	2	Carbamazepine	4
Atracurium	9	Carbimazole	2
Atropine	1	Carnitine	3
Augmentin Duo®	36	Cefepime	3
Augmentin Duo Forte®	7	Cefotaxime	10
Ceftazidime	1	Creon	9
Ceftriaxone	16	Cromoglycate	2
Cephalexin	21	Crotamiton	1

Drug Name	Frequency	Drug Name	Frequency
Cephazolin	15	Cyclopentolate	15
Cetaphil® cleanser	1	Cyclophosphamide	5
Cetylpyridinum chloride	1	Cyclosporin	1
Chloral hydrate	7	Cyproheptadine	1
Chloramphenicol	24	Darbapoetin alfa	1
Chlorhexidine	14	Demazin®	1
Chlorhexidine/ lignocaine	1	Dermeze®	5
Choline salicylate	4	Desmopressin	5
Ciclesonide	1	Detemir insulin	2
Ciprofloxacin	6	Dexamethasone	58
Ciproxin® HC	7	Dexchlorpheniramine	2
Cisplatin	1	Diazepam	8
Cisretinoic acid	1	Diclofenac	2
Clindamycin	4	Digoxin	1
Clobazam	3	Dilacaine	12
Clonazepam	7	Docusate	4
Clonidine	14	Domperidone	2
Clotrimazole	2	Dopamine	3
Codeine	12	Dornase alfa	3
Colecalciferol	5	Doxorubicin	1
Cophenylcaine	2	Doxycycline	1
Coenzyme Q10	1	Emla	26
Colonlytely®	1	Enalapril	3
Coloxyl with senna	5	Entonox	1
Cotrimoxazole	1	Epipen junior	5
Epipen	7	Griseofulvin	1
Escitalopram	1	Heparin	3
Esomeprazole	1	Hep B vaccine	3
Etonogestrel	1	Homatropine	1
Ectoposide	1	Humalog®	11
Erythromycin	2	Humulin® NPH	4

Drug Name	Frequency	Drug Name	Frequency
Fentanyl	39	Hyaluronidase	1
Ferrous sulfate	8	Hydralazine	2
Fess	1	Hydrochlorothiazide	1
Filgrastim	2	Hydrocortisone	20
Flucloxacillin	41	Hydroxyurea	1
Fluconazole	7	Hydrozole®	1
Fludrocortisone	2	Hyoscine butylbromide	3
Fluorometholone	1	Ibuprofen	201
Fluorouracil	1	Indomethacin	1
Fluoxetine	4	Infliximab	2
Fluticasone	7	Interferon beta	1
Folic acid	4	Ipratropium	14
Frusemide	7	Kenacomb®	4
Gabapentin	2	Ketamine	3
Gentamicin	21	Lactulose	21
Glargine insulin	11	Lamotrigine	12
Glucagon	4	Lansoprazole	3
Glucose	1	Latanoprost	2
Glycerin	5	Leuprorelin	1
Glyceryl trinitrate	2	Levonorgestrel	1
Glycopyrrolate	1	Levonorgestrel/ ethinyloestradiol	2
Gonadorelin	2	Levetiracetam	7
Levocabastine	1	Mixtard® insulin	1
Lignocaine	9	MMR, MenCCV and Hib	1
Liquid paraffin	5	Mometasone	16
Lisinopril	2	Montelukast	8
Locacorten® ear drops	1	Morphine	80
Loperamide	1	Movicol®	10
Loratadine	26	Moxifloxacin	1
Lorazepam	10	Mupirocin	8
Losartan	1	Mycophenolate	1

Drug Name	Frequency	Drug Name	Frequency
Magnesium chloride	2	Mycostatin	1
Mannitol	1	Mylanta	3
Melatonin	1	Naproxen	6
Mercaptopurine	1	Natalizumab	1
Meropenem	5	Nemdyn®	1
Mesalazine	2	Nifedipine	2
Mesna	2	Nitrazepam	1
Metformin	1	Nitric oxide	4
Methotrexate	4	Normal immunoglobulin	4
Methylphenidate	4	Normal saline	7
Methylprednisolone	11	Nurofen Plus®	1
Metoclopramide	26	Nystatin	10
Metolazone	1	Octreotide	1
Metoprolol	1	Oestradiol	1
Metronidazole	19	Ofloxacin	2
Microlax	5	Oily glycerol	1
Midazolam	31	Olanzapine	2
Minoxidil	1	Olopatadine	3
Mirtazapine	1	Omeprazole	18

Drug Name	Freq	Drug Name	Freq
Ondansetron	126	Polyvinyl alcohol	2
Oxcarbazepine	6	Potassium chloride	4
Oxybutynin	3	Praziquantel	2
Oxycodone	74	Prednefrin forte®	2
Painstop Day®	80	Prednisone	1
Painstop Night	9	Prednisolone	48
Panadeine	19	Pregabalin	1
Panadeine Forte	21	Prochlorperazine	1
Pancuronium	1	Promethazine	13
Pantoprazole	2	Propranolol	2
Paracetamol	314	Propofol	29
Parachoc	10	Propylthiouracil	1
Parecoxib	2	Protaphane®	9
Pegfilgrastim	3	Psyllium	2
Pentavite®	4	Quetiapine	4
Perindopril	1	Ranitidine	11
Pethidine	11	Rectinol®	2
Phenobarbitone	8	Rifampicin	1
Phenoxymethylpenicillin	10	Risperidone	1
Phenylephrine	1	Ropivacaine	1
Phenytoin	4	Roxithromycin	5
Phosphate	1	Salbutamol	58
Picibanil	1	Salicylic acid/ cetylpyridinum	1
Pimecrolimus	1	Senna	2
Piperacillin	1	Seretide®	9
Piroxicam	1	Sertraline	2
Pizotifen	7	Sildenafil	2
Poloxamer	4	Sodium bicarbonate	4

Drug Name	Frequency	Drug Name	Frequency
Sodium chloride	7	Tocilizumab	1
Sodium phosphate	3	Tolteridone	1
Sodium valproate	13	Topiramate	7
Solifenacin	2	Topotecan	2
Sofradex®	3	Tramadol®	3
Somatropin	4	Tranexamic acid	1
SOOV	1	Tretinoin	1
Sorbolene and paw paw	1	Triamcinolone	2
Spironolactone	1	Trichloracetic acid paste	1
Sumatriptan	1	Trimethoprim/ sulfamethoxazole	17
Suxamethonium	2	Tropisetron	6
Tacrolimus	3	Tropicamide	2
Teicoplanin	1	Valaciclovir	2
Temazepam	6	Valganciclovir	2
Terbinafine	1	Vancomycin	14
Terbutaline	2	Vecuronium	2
Testosterone	1	Vigabatrin	1
Tetanus booster	1	Vincristine	2
Tetanus vaccine	1	VitABDeck®	5
Tetracosatrin	2	Vitamin D3	2
Thalidomide	1	Vitamin E	1
Thioguanine	1	Vitamin K	4
Ticarcillin/ clavulanic acid	20	Voriconazole	1
Timolol	1	Warfarin	2
Tinidazole	2	Xalacom	1
Thyroxine	13	Xylocaine viscous	1
Tobramycin	10	Xylometazoline	6

Appendix 5 - Calculation of lincomycin content in Lincocin® injection solution

The lincomycin content in Lincocin® injection solution was calculated using the equation from the calibration curve:

Peak Area = 17.832x + 0.24572

12.974856 = 17.832x + 0.24572

x = 0.7138 mg/mL

molecular weight of lincomycin hydrochloride monohydrate = 461.02

molecular weight of lincomycin base = 406.54

weight of lincomycin in

0.6 mg/mL sample = 0.7138 mg/mL (406.54 / 461.02)

= 0.629 mg

Hence 0.6294806 mg would have been in 1 mL

so in 200 mL, there would have been 125.8961 (which was actually initially in the 0.4 mL)

So 125.8961 in 0.4 mL = 31.474 mg/ 0.1 mL = 314.74 mg/mL

Each Lincocin® injection is stated to contain 300mg lincomycin base per mL, so percentage error

$$= \frac{14.74}{300} \times 100$$

= 4.91344%

= 4.9% or 104.9% of lincomycin

Appendix 6 - Details of off-label and unlicensed cases included in the study.

(ID = identification; IP = inpatient; OP = outpatient; ED = Emergency Department patient; Reg = registered; Lic = licensed; OL = off-label; UL = unlicensed).

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
61	19 d	3.72	M	IP	Possible viral meningitis. Red rash on forehead, stomach & legs	aciclovir	77mg tds	IV	IV	yes	no	OL	Age	MIMS/ TGA: No dosage given for children < 1 year
372	4 w	4.33	M	OP	Review of possible viral meningitis.	aciclovir	93mg tds	IV	IV	yes	no	OL	Age	MIMS/ TGA: No dosage given for children < 1 year
714	0 d	3.18	M	IP	Hypoxic ischaemic neonatal encephalopathy with meconium aspiration and seizures	aciclovir	65 mg tds	IV	IV	yes	no	OL	Age	MIMS/ TGA: No dosage given for children < 1 year
945	10 m	8.6	M	ED	Impetigo	aciclovir	100 mg	IV	IV	yes	no	OL	Age	MIMS/ TGA: No dosage given for children < 1 year
949	4 y		M	ED	Diarrhoeal illness, hypoglaecemic episode, ulcers on buccal surface and palate	aciclovir	200 mg 5x / day	Tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established
63	2 y	14.1	M	IP	Bronchiectasis (confirmed on a CT scan). Recently moved to Australia from Tanzania. PMH includes 2 episodes of pneumonia and mannose binding lectin (MBL) deficiency.	adrenaline	0.75mL inhaled	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL
78	15 y		M	ED	Possible capillary hemangioma	adrenaline	1.5 mL diluted to 20 mL applied topically	IV	Topical	yes	no	OL	ROA	Solution for injection used topically. MIMS states indication as adjunctive use in the management of cardiac arrest.
98	1 y 8 m		M	ED	Possible croup (marked stridor and recession)	adrenaline	0.5mL inhaled	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL
418	1.5 y		M	ED	Viral induced wheeze. (Patient unwell for 2 days and has runny nose, cough, difficulty breathing and no stridor at that time)	adrenaline	0.6mL inhaled	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL
429	2 y	11.5	M	ED	Croup. R upper lobe anterior segment bronchomalacia,bronchiectasis. Presented with a day's Hx of URTI Sx and stridor. CXR demonstrated patchy changes consistent with viral LRTI.	adrenaline	nebulised	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	adrenaline	0.4ml twice	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL
797	**5 y**	**18.65**	**M**	**IP**	Allergic reaction	adrenaline	1%	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL
880	**1 y**		**M**	**IP**	Severe croup, asthma; transferred from JHC	adrenaline	5 mg	resp sol	Inhaled	no	no	UL	Formulation	PMH formulation - Adrenaline 1% Respirator Solution 15 mL
1	**9 y**		**M**	**IP**	Injury - fell off a push bike and lost 200ml of blood. Patient was taken to theatre for wound exploration and repair.	alfentanil	1mg	injection	IV	yes	no	OL	Age	MIMS: Adequate data to support the use of alfentanil in children under 12 years of age are presently not available.
414	**7 y**	**47.85**	**M**	**ED**	Appendicitis. Patient was admitted for laparoscopic appendectomy.	alfentanil	1mg	IV	IV	yes	no	OL	Age	MIMS: Adequate data to support the use of alfentanil in children under 12 years of age are presently not available.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	alteplase	1 mL	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of Actilyse in children have not been established. Therefore, treatment of such patients is not recommended
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	alteplase	0.5 mg	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of Actilyse in children have not been established. Therefore, treatment of such patients is not recommended
936	**17 y**	**55.55**	**F**	**OP**	Major depressive disorder, chronic costochondritis	amitriptylline	25 mg nocte	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy of Endep for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Endep should not be used in this age group for the treatment of depression
1137	**1 y 3 m**	**9.6**	**M**	**OP**	Review for liver transplanted	amlodipine	1.6 ml daily	liquid	PO	yes	no	OL	Age	MIMS: Safety and effectiveness have not been established in children. Also, no oral liquid formulation available so PMH prepared formulation
61	**19 d**	**3.72**	**M**	**IP**	Possible viral meningitis. Red rash on forehead, stomach & legs	amoxicillin	220mg tds	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
185	**2 m**	**4.02**	**F**	**IP**	Gastroenteritis (Vomiting and diarrhoea and patient treated for presumed sepsis)	amoxicillin	200mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
186	**27 d**	**4.34**	**M**	**OP**	Possible of sepsis	amoxicillin	215mg	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
205	**5 y**	**19.75**	**M**	**IP**	Adenoidectomy and cautery of turbinates	amoxicillin	1.5g	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
257	1.5 y		F	ED	Cellulitis (MRSA); 12 hours of fever, vomit, rash to abdomen. Ringworm found around buttock	amoxicillin	315mg q8h	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
371	20 d	3.57	M	IP	Possible sepsis - admitted for a septic screen including blood cultures, and CXR.	amoxicillin	175mg	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
371	20 d	3.57	M	IP	Possible sepsis - admitted for a septic screen including blood cultures, and CXR.	amoxicillin	180mg QID	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
372	6 d	4.33	M	IP	Possible viral meningitis.	amoxicillin	233mg tds	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
438	5 y	19	F	IP	Post-tonsillectomy bleed - adenotonsilectomy conducted 16 days ago.	amoxicillin	300mg QID	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
527	1 m	3.04	M	IP	Complex congenital cyanotic heart disease, pulmonary hypertension	amoxicillin	180 mg qid	NGT	NGT	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
635	1 m 5 d	3.3	F	IP	Gastroschisis	amoxicillin	150 mg tds = 136 mg/kg/day	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
689	27 d	3.31	F	IP	Abdominal distension (likely secondary to air swallowing)	amoxicillin	165mg once	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
769	3 d	4.43	M	IP	Mildly dilated ascending aorta, biventricular hypertrophy, laryngomalacia with laryngeal reflux	amoxicillin	235 mg tds	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
858	1 y 8 m		F	ED	Mild pneumonia	amoxicillin	150 mg tds 7/7	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
994	2 d	2.04	M	IP	Necrotising enterocolitis, short bowel syndrome	amoxicillin	105 mg bd	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
1024	4 d	2.77	M	IP	Trachoesophageal fistula repair, GORD	amoxicillin	129 mg tds	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.
1073	4 y		F	OP	Sacral agenesis L5/S1 nerve roots; UTI prophylaxis, urinary continence	amoxicillin	250 mg nocte	liquid		yes	no	OL	Indication	MIMS: Not registered for UTI prophylaxis
1199	1 y 10 m	11.9	M	IP	Neck abscess, drainage	amoxicillin	300 mg tds 7/7	tds	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 20kg: 20-40mg/kg/day in divided doses every 6-8 hours.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
591	**17 y**	**75.2**	**M**	**IP**	High risk T-cell ALL	aprepitant	80 mg	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness of Emend in paediatric patients have not been established. The pharmacokinetics of Emend have not been evaluated in patients below 18 years.
804	**14 y**		**M**	**IP**	Burkitt's lymphoma	aprepitant	80 mg	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness of Emend in paediatric patients have not been established. The pharmacokinetics of Emend have not been evaluated in patients below 18 years.
1197	**13 y**	**44.1**	**M**	**IP**	Nasopharyngeal carcinoma, PEG insertion	aprepitant	80 mg	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness of Emend in paediatric patients have not been established. The pharmacokinetics of Emend have not been evaluated in patients below 18 years.
339	**1 y**	**9.6**	**M**	**ED**	Osteomylitis and pneumonia (staph aureus). Other diagnoses included pneumothorax, gardia and thrombocytosis.	aspirin	30mg	oral	PO	no	no	UL	Formulation	No oral liquid formulation available; hospital formulation.
1137	**1 y 3 m**	**9.6**	**M**	**OP**	Review for liver transplanted	aspirin	1.3 ml daily	liquid	PO	no	no	UL	Formulation	No oral liquid formulation available; hospital formulation.
725	**8 y**	**26.6**	**F**	**IP**	Chronic nephropathy	atorvastatin	20 mg daily	tab	PO	yes	no	OL	Age	MIMS: Treatment experience in a paediatric population is limited. Pharmacokinetic studies have not been conducted in the paediatric population.
665	**2 w**		**M**	**IP**	Conjunctivitis	amoxicillin and clavulanic acid	100 mg bd 7/7	liquid	PO	yes	no	OL	Age	MIMS: No dosage given for children < 2 months
944	**1 y**	**8.68**	**F**	**IP**	Bronchiolitis, LRTI	amoxicillin and clavulanic acid	225 mg bd 1/52	liquid	PO	yes	no	OL	Dose	Greater dose than specified in MIMS. MIMS: Children 2 mths - 12 yrs < 40 kg (mod-severe infection): 45 mg/kg/day in 2 divided doses.
1148	**27 d**	**4.15**	**M**	**IP**	UTI	amoxicillin and clavulanic acid	96 mg bd	liquid	PO	yes	no	OL	Age	MIMS: No dosage given for children < 2 months
844	**9 y**		**M**	**OP**	Renal transplant, hypertension, epilepsy, chronic diarrhoea, metaphysical dysplasia	azathioprine	15 mg daily (10mg/mL)	liquid	PO	no	no	UL	Formulation	No oral liquid formulation available; hospital formulation.
1137	**1 y 3 m**	**9.6**	**M**	**OP**	Review for liver transplanted	azathioprine	1.35 ml daily	liquid	PO	no	no	UL	Formulation	No oral liquid formulation available; hospital formulation.
532	**13 y**	**50.5**	**M**	**OP**	Cystic fibrosis, pancreas insufficiency and bronchiectasis	azithromycin	250 mg daily	tab	PO	yes	no	OL	Indication	MIMS: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
527	**1 m**	**3.04**	**M**	**IP**	Complex congenital cyanotic heart disease, pulmonary hypertension	benzylpenicillin	120 mg tds	IV	IV	yes	no	OL	Dosage	MIMS: Neonates: 30-60 mg every 12 hours; children < 3 years: 60 mg 6 hourly.
945	**10 m**	**8.6**	**M**	**ED**	Impetigo.	benzylpenicillin	520 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children < 3 years minimum dose of 60 mg 6 hourly; children 3 - 10 years: 150 to 300 mg 6 hourly.
73	**8 y**		**F**	**OP**	Alopecia areata. Eczema around eyes and elbows.	betamethasone	daily	ointment	Topical	yes	no	OL	Age	MIMS: Diprosone OV is not recommended for use in children under 12 years of age.
306	**9 y**		**M**	**OP**	Eczema - severe on palms and localized areas such as soles.	betamethasone	apply sparingly daily to hands and feet	ointment	Topical	yes	no	OL	Age	MIMS: Diprosone OV is not recommended for use in children under 12 years of age.
333	**9 y**		**M**	**OP**	Traumatic mydriasis and scleral perforation. Had stick thrown in R eye; injured orbit.	betaxolol	1 drop bd	eye drops	Eye drops	yes	no	OL	Age	MIMS: Clinical studies to establish the safety and efficacy in children have not been performed
333	**9 y**		**M**	**OP**	Traumatic mydriasis and scleral perforation. Had stick thrown in R eye; injured orbit.	brimonidine	Dose not specified	eye drops	Eye drops	yes	no	OL	Age	Mims: Safety and effectiveness of brimonidine in paediatric patients has not been established.
333	**9 y**		**M**	**OP**	Traumatic mydriasis and scleral perforation. Had stick thrown in R eye; injured orbit.	brinzolamide	1 drop bd	eye drops	Eye drops	yes	no	OL	Age	MIMS: The safety and effectiveness of Azopt eye drops in paediatric patients have not been established
1170	**7 y**	**24.2**	**F**	**OP**	Asthma, allergic rhinitis	budesonide/ eformoterol	2 puffs bd; 100/6 mcg	puffs	Inhaled	yes	no	OL	Age	MIMS: Symbicort is not recommended for children below 12 years of age.
725	**8 y**	**26.6**	**F**	**IP**	Chronic nephropathy	calcium carbonate	600 mg bd	tab	PO	yes	no	OL	Age	MIMS: No children's dosage listed.
844	**9 y**		**M**	**OP**	Renal transplant, hypertension, epilepsy, chronic diarrhoea, metaphysical dysplasia	captopril	2.5 mg tds	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established.
896	**2 m**		**M**	**OP**	Neonatal hypothyroidism due to maternal antibodies	carbimazole	1 mg tds	liquid	PO	yes	no	OL	Age	MIMS/TGA: No paediatric dosage listed; hospital formulated capsules?
642	**4 y**		**F**	**OP**	CP, glutaric aciduria type I, OSA, GORD	carnitine	450 mg	liquid	PO	no	no	UL	Formulation	Carnitine liquid not registered in Australia.
746	**1 m**		**F**	**IP**	Glutamic aciduria	carnitine	70 mg tds	liquid	PO	no	no	UL	Formulation	Carnitine liquid not registered in Australia.
812	**6 y**	**25**	**F**	**IP**	Epilepsy, seizure with cyanotic episode, admitted after seen in ED; deceased 9/5/2010 (apnoea following LRTI and seizure)	carnitine	300 mg bd	liquid	PO	no	no	UL	Formulation	Carnitine liquid not registered in Australia.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
257	**1.5 y**	**12.7**	**F**	**ED**	Cellulitis (MRSA); 12 hours of fever, vomit, rash to abdomen. Ringworm found around buttock	cephalexin	250mg QID	oral	PO	yes	no	OL	Dose	Greater dose than specified in MIMS. MIMS: The usual recommended daily dose for children is 25-50mg/kg in divided doses. Child 10kg: 5-10mL bd of 125mg/5mL suspension.
1073	**4 y**		**F**	**OP**	Sacral agenesis L5/S1 nerve roots; UTI prophylaxis, urinary continence	cephalexin	200 mg nocte	liquid	PO	yes	no	OL	Indication	MIMS: Not registered for UTI prophylaxis.
665	**2 w**		**M**	**IP**	Conjunctivitis	cephazolin	1 drop to RE q2h	eye drop	Eye drops	no	no	UL	Formulation	Hospital formulation.
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	chloral hydrate	350 mg qid prn	liquid	PO	yes	no	OL	Indication	MIMS: Only indicated for preop sedation and short-term treatment of insomnia (< 2 wks); Chloral Hydrate Mixture is not recommended in infants and children when repetitive dosing would be necessary
880	**1 y**		**M**	**IP**	Severe croup, asthma; transferred from JHC	chloral hydrate	80 mg qid prn	liquid	PO	yes	no	OL	Indication	MIMS: Only indicated for preop sedation and short-term treatment of insomnia (< 2 wks); Chloral Hydrate Mixture is not recommended in infants and children when repetitive dosing would be necessary
1116	**3 m**	**4.84**	**F**	**IP**	Cleft lip repair	chloral hydrate	300 mg	liquid	PO	yes	no	OL	Dose	MIMS: Children: 30-50mg/kg or 1.5g/m2, max 1g.
281	**3 y**		**M**	**IP**	Biopsy of a lesion on forehead under general anaesthesia	chloramphenicol	apply sparingly for 7 days daily	eye ointment	Topical	yes	no	OL	Indication	MIMS: Chloramphenicol eye ointment is only indicated for ocular bacterial infections caused by organisms susceptible to chloramphenicol.
516	**2 y**	**9.6**	**M**	**OP**	Replantation of left thumb	chloramphenicol	10 mg/g qid to left thumb	eye ointment	Topical	yes	no	OL	Indication	MIMS: Chloramphenicol eye ointment is only indicated for ocular bacterial infections caused by organisms susceptible to chloramphenicol.
543	**10 m**		**M**	**ED**	Balanitis	chloramphenicol	10 mg/g topical	eye ointment	Topical	yes	no	OL	Indication	MIMS: Chloramphenicol eye ointment is only indicated for ocular bacterial infections caused by organisms susceptible to chloramphenicol.
819	**1 y**	**11.65**	**M**	**IP**	Eyebrow laceration (infected), finger infection	chloramphenicol	10 mg/g qid to wound	eye ointment	Topical	yes	no	OL	Indication	MIMS: Chloramphenicol eye ointment is only indicated for ocular bacterial infections caused by organisms susceptible to chloramphenicol.
1101	**2 y**	**11.7**	**M**	**IP**	Hydronephrosis, iron deficiency anaemia	ciprofloxacin	110 mg bd	IV	IV	yes	no	OL	Age	MIMS: Ciprofloxacin is not recommended for use in prepubertal children, except for use in inhalational anthrax (postexposure).
717	**13 y**	**46.85**	**M**	**IP**	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	cisretinoic acid			IV			UL	SAS	Not registered in Australia

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
789	**9 y**		**M**	**OP**	Cognitive impairment, epilepsy, significant behavioural problems, non-verbal	clobazam	5 - 7.5 mg bd	tab	PO	yes	no	OL	Age	MIMS: Not recommended for children
884	**1 y 3 m**	**12.8**	**F**	**IP**	Hyponatraemia, seizures, left ventricular cyst (VP shunt), panhypothyroidism, diabetes insipidus, septo-optic dysplasia	clobazam	2.5 mg	liquid	PO	yes	no	OL	Age	MIMS: Not recommended for children. No liquid formulation available - hospital formulation
1001	**2 y**		**M**	**OP**	Epilepsy, strabismus	clobazam	2.5 mg (1/4 tab) prn clusters	tab	PO	yes	no	OL	Age	MIMS: Not recommended for children
104	**2 y**	**15**	**M**	**IP**	Dentinogenesis imperfecta (Patient admitted for dental restoration and extraction)	clonidine	30mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
115	**15 y**	**35.9**	**M**	**OP**	Epilepsy, aggressive behaviour and learning problems.	clonidine		IV	IV	yes	no	OL	Indication	MIMS: Hypertension. Injection indicated for acute hypertensive crisis. Not indicated for aggressive behaviour or attention deficit disorder
132	**5 y**	**18.2**	**F**	**IP**	Adenotonsillectomy	clonidine	20mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
390	**6 y**	**20**	**F**	**IP**	Adenotonsillectomy	clonidine	15mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
399	**7 y**	**42.2**	**M**	**IP**	Myringotomy, insertion of grommets and adenoidectomy	clonidine	30mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
458	**9 y**	**37.3**	**F**	**IP**	Tonsillectomy	clonidine	40mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
523	**1 y**		**M**	**IP**	Subcoronal hypospadias repair	clonidine	45 mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
572	**11 y**	**47.2**	**M**	**IP**	Excision of congenital melanocytic nevus on left posterior thigh	clonidine	120 mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
815	**10 y**		**F**	**ED**	Autistic disorder, severe behavioural disturbance	clonidine	100 mcg bd	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
833	**8 y**	**22.8**	**M**	**IP**	Mosaic down syndrome, left tibial osteotomy and fibular epiphyseodesis, constipation	clonidine	80 mcg	IV	IV	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
1090	**10 y**		**F**	**OP**	ADHD	clonidine	100 mcg nocte	tab	PO	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis. Not indicated for aggressive behaviour or attention deficit disorder
1091	**12 y**		**F**	**OP**	ADHD	clonidine	100 mcg nocte	tab	PO	yes	no	OL	Indication	MIMS: Hypertension. Injection indicated for acute hypertensive crisis. Not indicated for aggressive behaviour or attention deficit disorder
1095	**5 y**	**20.3**	**M**	**IP**	Left-sided cochlear implant, seasonal allergic rhinitis	clonidine	100 mcg	tab	PO	yes	no	OL	Age	MIMS: Hypertension. Injection indicated for acute hypertensive crisis - no suggestion that it can be used in this age group. Used here for sedation/anaesthesia
183	**1 y**	**10.1**	**F**	**IP**	Left upper limb injury, finger trapped and nail avulsed.	codeine	5-10mg q4h prn	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
218	**5 m**	**6.5**	**M**	**IP**	Possible bronchiolitis	codeine	5mg	liquid	PO	yes	no	OL	Age	MIMS: No children's dose.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	codeine	8-16 mg	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	codeine	2 mg	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
814	**6 m**	**9.35**	**M**	**IP**	Removal of bilateral preauricular skin tags and removal anterior tongue cyst	codeine	4-8 mg q4h prn	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
832	**12 y**	**43**	**F**	**IP**	Intrinsic brain stem glioma; deceased 17.12.08	codeine	30 mg qid prn	liquid	PO	yes	no	OL	Indication	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu.
862	**7 m**	**9.9**	**M**	**IP**	Vomiting, fever, irritability,	codeine	2.5 mg qid	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
886	**3 y**		**M**	**IP**	Adenotonsillectomy	codeine	10-15 mg q4h prn	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	codeine	15-30 mg	tab	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
1116	**3 m**	**4.84**	**F**	**IP**	Cleft lip repair	codeine	2 mg qid prn	liquid	PO	yes	no	OL	Age	MIMS: Codeine linctus is indicated for an unproductive, dry and intractable cough associated with colds and flu. No children's dose.
844	**9 y**		**M**	**OP**	Renal transplant, hypertension, epilepsy, chronic diarrhoea, metaphysical dysplasia	darbepoetin alfa	60 mcg fortnightly	SC	SC	yes	no	OL	Age	MIMS: The safety and efficacy of Aranesp (darbepoetin alfa) in paediatric patients have not been established.
63	**2 y**	**14.1**	**M**	**IP**	Bronchiectasis (confirmed on a CT scan). Recently moved to Australia from Tanzania. PMH includes 2 episodes of pneumonia and mannose binding lectin (MBL) deficiency.	dexamethasone	2.25mg daily for 2 days	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
98	**1 y 8 m**		**M**	**ED**	Possible croup (marked stridor and recession)	dexamethasone	1.7mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
138	**2 y 5 m**		**M**	**ED**	Possible croup	dexamethasone	2.25mg	oral	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
164	**2 y**	**11.3**	**M**	**ED**	Respiratory distress - croup. Hx of asthma	dexamethasone	1.65mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
227	**5 y 8 m**	**34.6**	**M**	**ED**	Respiratory symptoms - sore throat, fever, painful swallowing	dexamethasone	4mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
278	**7 y**		**M**	**IP**	Croup (Symptoms included sore throat, fever and not being able to breathe)	dexamethasone	3.2mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
415	**9 m**		**M**	**IP**	Croup (Respiratory distress)	dexamethasone	1.6mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
418	**1.5 y**		**M**	**ED**	Viral induced wheeze. (Patient unwell for 2 days and has runny nose, cough, difficulty breathing and no stridor at that time)	dexamethasone	7.2mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
429	**2 y**	**11.5**	**M**	**ED**	Croup. R upper lobe anterior segment bronchomalacia and bronchiectasis. Day's Hx of URTI Sx and stridor. CXR demonstrated patchy changes consistent with viral LRTI.	dexamethasone	1.65mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
444	**10 m**		**M**	**ED**	Viral URTI (dry cough, runny nose)	dexamethasone	1.2mg	oral liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
548	**1 y 10 m**		**M**	**ED**	Croup, respiratory distress	dexamethasone	1.9 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
727	**7 y**		**F**	**ED**	Fever, cough, sore throat, croupy cough, viral URTI	dexamethasone	3.6 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
741	**1 y 5 m**		**F**	**ED**	Respiratory distress, croupy cough, stridor	dexamethasone	2 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
895	**8 m**		**F**	**ED**	Viral illness	dexamethasone	1.4 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
901	**4 y**		**M**	**ED**	Viral illness, respiratory distress, croup	dexamethasone	4.2 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
1004	**2 y**	**13.76**	**M**	**ED**	Cough, asthma, URTI, viral illness	dexamethasone	2 mg daily 2/7	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
1011	**3 y**		**F**	**ED**	Viral croup	dexamethasone	1.5 mg daily prn	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
1028	**1 y 9 m**		**M**	**IP**	Croup	dexamethasone	2 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
1080	**4 y**		**M**	**ED**	Croup, rash	dexamethasone	3 mg	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
1138	**1 y**		**F**	**ED**	Croup	dexamethasone	1.8 mg daily 2/7	liquid	PO	no	no	UL	Formulation	PMH formulation - Dexamethasone Oral Solution 1mg/mL
333	**9 y**		**M**	**IP**	Traumatic mydriasis and scleral perforation. Had stick thrown in R eye; injured orbit.	dexamethasone	1 drop qid	eye drops	Eye drops	yes	no	OL	Age	MIMS/ TGA: The safety and effectiveness of Maxidex eye drops in paediatric patients have not been established
637	**5 y**		**F**	**OP**	Allergic rhinoconjunctivis.	dexamethasone	1 drop tds BE; 1 mg/ml	eye drop	Eye drops	yes	no	OL	Age	MIMS/ TGA: The safety and effectiveness of Maxidex eye drops in paediatric patients have not been established
695	**2 y**		**F**	**IP**	Bilateral esotropia	dexamethasone	1 drop 1 mg/ml tds BE	eye drops	Eye drops	yes	no	OL	Age	MIMS/ TGA: The safety and effectiveness of Maxidex eye drops in paediatric patients have not been established
976	**10 y**		**M**	**IP**	Bilateral epiblepharon repair	dexamethasone	1 mg/ml qid BE	eye drops	Eye drops	yes	no	OL	Age	MIMS/ TGA: The safety and effectiveness of Maxidex eye drops in paediatric patients have not been established
1105	**1 y 8 m**	**13.7**	**M**	**IP**	Right 4th nerve palsy, oblique myectomy	dexamethasone	1 mg/ml qid right eye	eye drop	Eye drops	yes	no	OL	Age	MIMS/ TGA: The safety and effectiveness of Maxidex eye drops in paediatric patients have not been established
1185	**4 m**		**M**	**OP**	Glaucoma, left exotropia	dexamethasone	1 mg/ml tds BE	eye drops	Eye drops	yes	no	OL	Age	MIMS/ TGA: The safety and effectiveness of Maxidex eye drops in paediatric patients have not been established
264	**3 m**		**F**	**OP**	Possible retinopathy of prematurity	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
370	7 m		F	OP	Primary lymphoedema (Miliary syndrome)	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
524	11 m		F	OP	Retinopathy exam, bronchiolitis	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
526	3 m	5.08	F	OP	Beckwith-Wiedemann syndrome, cutaneous heamangioma, hepatic haemangioma	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
629	6 m		F	OP	Pre-term ophthalmic review	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
630	6 m		M	IP	Facial bruising (observation)	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
648	7 y		M	OP	Ophthalmic clinic review	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
743	5 m		F	OP	Ophthalmic review	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
744	3 m		M	OP	Ophthalmic review	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
807	7 m	5.26	F	IP	CP, seizures and spasms, lissencephaly	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
1050	1 y		M	OP	Buthalmus, right sided proptosis, hypoglobus lagophthalmus	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
1114	10 m		F	OP	Squint both eyes	dilacaine	1 drop	eye drop	Eye drops	no	no	UL	Formulation	PMH formulation - Dilacaine Eye Drops
538	1 y 3 m	8.22	F	OP	Gastric reflux, feeding difficulties	domperidone	2 mg bd	liquid	PO	no	no	UL	Formulation	PMH formulation - Domperidone Oral Suspension
1112	8 m	5.34	M	ED	Bronchiolitis	domperidone	1 mg tds	liquid	PO	no	no	UL	Formulation	PMH formulation - Domperidone Oral Suspension
485	1 y		M	OP	Review of coarction repair and duct litigation.	dopamine	1mL / hour	IV	IV	yes	no	OL	Age	MIMS: It is not recommended for use in children as safety and efficacy in this age group have not been established.
714	newborn	3.18	M	IP	Hypoxic ischaemic neonatal encephalopathy with mecorium aspiration and seizures	dopamine	190 mg	IV	IV	yes	no	OL	Age	MIMS: It is not recommended for use in children as safety and efficacy in this age group have not been established.
1024	4 d	2.77	M	IP	Trachoesophageal fistula repair, GORD	dopamine	79 mg daily 3/7	IV	IV	yes	no	OL	Age	MIMS: It is not recommended for use in children as safety and efficacy in this age group have not been established.
514	2 y	11.3	M	OP	Multiple food allergies	epipen jr.	0.15 mg prn	IM	IM	yes	no	OL	Age	MIMS: EpiPen Jr is intended for children with body weight of 15 to 30 kg
114	14 y	55	M	IP	Injury after playing football. Also suicidal ideation and worsening depression.	escitalopram	20mg daily	oral	PO	yes	no	OL	Age	MIMS: The efficacy and safety of escitalopram have not been established in children and adults less than 18 years of age.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
88	**1 y**	**11.4**	**F**	**ED**	Injury-left upper limb. (patient was admitted for exploration and repair)	fentanyl	Dose: 15-10-10	solution	Intranasal	yes	no	OL	Age	MIMS: Safety of fentanyl in chn younger than 2 years of age has not been establishes. Also, fentanyl IV fluid is administered intranasally
205	**5 y**	**19.75**	**M**	**IP**	Adenoidectomy and cautery of turbinates	fentanyl	30mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
332	**3 y**	**16.05**	**M**	**OP**	Injury. Right upper limb and thumb fractured	fentanyl	15mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
357	**6 y**		**M**	**IP**	Otitis media and nasal obstruction	fentanyl	25mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
358	**6 y**	**26.45**	**M**	**ED**	Injury - closed fracture	fentanyl	40 mcg - one dose in ED	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
404	**15 y**		**M**	**ED**	Injury - fractured hand and swollen 2nd MCP joints	fentanyl	110 mcg - one dose in ED	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
413	**11 y**		**M**	**ED**	Fractured left wrist (swelling and pain of forearm)	fentanyl	45 mcg - one dose in ED	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
420	**15 y**		**F**	**IP**	Cerebral palsy (patient admitted for Botox injections)	fentanyl	100 mcg - one dose in ED	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
545	**15 y**		**M**	**OP**	Fractured left ankle	fentanyl	105 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
601	**11 y**		**M**	**IP**	Cerebral palsy, mild spastic dysplegia, focal epilepsy (btx-injections)	fentanyl	50 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
602	**10 y**		**F**	**ED**	Abdominal pain, central, radiating to back	fentanyl	44 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
703	**13 y**		**M**	**IP**	Laceration to perianal area, wound infection	fentanyl	75 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
717	**13 y**	**46.85**	**M**	**IP**	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	fentanyl	70 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
719	**11 y**		**M**	**ED**	Injury, left lower leg fracture	fentanyl	50 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
831	**10 y**	**38.4**	**F**	**IP**	Chronic recurrent multifocal osteomyelitis, pain management	fentanyl	55 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
836	**16 y**		**M**	**IP**	Orbital floor fracture, eye trauma, dizzy, nausea	fentanyl	100 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
909	**4 y**		**F**	**ED**	Vulva laceration	fentanyl	31 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
918	**13 y**	**62.3**	**M**	**IP**	Fractured left distal radius and ulna	fentanyl	250 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
926	**11 y**		**M**	**ED**	Fracture distal radius and ulna	fentanyl	90 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
1039	**8 y**		**M**	**ED**	Eye injury, swelling	fentanyl	50 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
1100	**4 y**	**17.15**	**M**	**IP**	Supracondylar elbow fracture	fentanyl	26 mcg	solution	Intranasal	yes	no	OL	ROA	Fentanyl IV fluid was administered intranasally. MIMS: Fentanyl injection is for intramuscular or intravenous injection only.
127	**8 y**	**42.9**	**M**	**ED**	Infection/inflammation of little toe - swelling, and boil like lesions on the inner aspects of leg-thigh.	flucloxacillin	2000mg six hourly for 1 day	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
155	**5 y**	**20**	**M**	**ED**	Acute lymphadenitis (presented with a 3 day history of limited neck movement and pain)	flucloxacillin	300mg QID for 1 week was changed after 2 days to 500mg QID	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: 250 mg every 6 hours; children 2-10 yrs: 1/2 adult dose.
257	**1.5 y**		**F**	**ED**	Cellulitis (MRSA); 12 hours of fever, vomit, rash to abdomen. Ringworm found around buttock	flucloxacillin	550mg six hourly	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
339	**1 y**	**9.6**	**M**	**ED**	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	flucloxacillin	500mg six hourly	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
587	**6 y**	**20.7**	**F**	**ED**	Right-sided pneumonia with pleural effusion.	flucloxacillin	1g QDS	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
605	**8 y**	**34.5**	**F**	**IP**	Cellulitis to ear.	flucloxacillin	1.7g QDS	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
819	**1 y**	**11.65**	**M**	**IP**	Eyebrow laceration (infected), finger infection.	flucloxacillin	275 mg qid 7/7	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: 250 mg every 6 hours; children 2-10 yrs: 1/2 adult dose.
819	**1 y**	**11.65**	**M**	**IP**	Eyebrow laceration (infected), finger infection.	flucloxacillin	500 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
824	**4 y**	**15.5**	**M**	**IP**	Periorbital cellulitis, laceration to eye glued on Sunday, swelling started Monday.	flucloxacillin	750 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
900	**4 y**		**M**	**IP**	Orbital cellulitis, chronic runny nose, right pansinusitis.	flucloxacillin	720 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
945	**10 m**	**8.6**	**M**	**ED**	Impetigo.	flucloxacillin	430 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
958	**5 y**	**17**	**M**	**ED**	Head injury, laceration of forehead.	flucloxacillin	850 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
1025	**5 y**		**F**	**IP**	Right tibia, low trauma fracture, skin lesions.	flucloxacillin	275 mg qid 7/7	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: 250 mg every 6 hours; children 2-10 yrs: 1/2 adult dose.
1025	**5 y**		**F**	**IP**	Right tibia, low trauma fracture, skin lesions.	flucloxacillin	1000 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
1126	**4 y**	**15.9**	**F**	**ED**	Acute OM, cellulitis finger.	flucloxacillin	400 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: 250 mg every 6 hours; children 2-10 yrs: 1/2 adult dose.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1166	**8 y**	**29.4**	**M**	**IP**	Right post septal abscess secondary to sinogesic source (nose).	flucloxacillin	1000 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
1199	**1 y 10 m**	**11.9**	**M**	**IP**	Neck abscess, drainage.	flucloxacillin	600 mg qid	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: IVI 250mg-1g every 6 hours. Severe infections may double dose. Children 2-10 yrs: 1/2 adult dose. Children < 2 yrs: 1/4 adult dose.
1199	**1 y 10 m**	**11.9**	**M**	**IP**	Neck abscess, drainage.	flucloxacillin	300 mg qid	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults: 250 mg every 6 hours; children 2-10 yrs: 1/2 adult dose.
283	**3 y**		**M**	**OP**	HSV ulceration of the cornea. Pain/sensitive to light - patient treated for blepharitis for many months.	fluorometholone	1 drop QID	gutt	Eye drops	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established.
1197	**13 y**	**44.1**	**M**	**IP**	Nasopharyngeal carcinoma, PEG insertion	5-fluorouracil	1400 mg	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Admin based on patients actual bodyweight (use ideal weight if obese, oedema); max 1 g/day.
65	**17 y**		**F**	**OP**	Eating disorder and exercise obsession.	fluoxetine	40mg daily	caps	PO	yes	no	OL	Age	MIMS: The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age have not been established
193	**14 y**	**42**	**F**	**IP**	Post-traumatic disorder. Showed depressive features and multi-sensory hallucinations.	fluoxetine	20mg	caps	PO	yes	no	OL	Age	MIMS: The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age have not been established
313	**14 y 5 m**		**M**	**OP**	Drug misuse, social isolation and behavioural issues	fluoxetine	40mg daily	caps	PO	yes	no	OL	Age	MIMS: The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age have not been established
835	**17 y**		**M**	**ED**	Non-epileptic seizures, migraine, anxiety disorder	fluoxetine	20 mg bd	caps	PO	yes	no	OL	Age	MIMS: The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age have not been established
673	**13 y**		**F**	**IP**	Left-sided facio-auriculo vertebral spectrum, complex congenital heart disease, end stage cardiac failure with cachexia; deceased 07/02/09, at home	gabapentin	100 mg daily	tab	PO	yes	no	OL	Age	MIMS: Neuropathic pain: Safety and effectiveness in children below the age of 18 years have not been established.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
923	**15 y**		**F**	**IP**	Spondylo-epiphyseal dysplasia tarda pseaudorheumatoid arthritis; scoliosis, spinal fusion	gabapentin	300 mg nocte 10/7	tab	PO	yes	no	OL	Age	MIMS: Neuropathic pain: Safety and effectiveness in children below the age of 18 years have not been established.
91	**7 y**	**26**	**M**	**IP**	Acute appendicitis with perforation, admitted for laparoscopic appendectomy.	gentamicin	195mg daily once	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
498	**16 y**		**M**	**IP**	Hodgkin Lymphoma (diagnosed in 2006)	gentamicin	330mg single daily dose	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
500	**11 y**	**47.2**	**M**	**ED**	Severe abdominal pain. Patient was diagnosed with acute appendicitis and underwent urgent appendectomy.	gentamicin	350mg daily once	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
667	**8 m**	**9.95**	**M**	**IP**	UIT, *E.coli*	gentamicin	68 mg once daily	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
689	**27 d**	**3.31**	**F**	**IP**	Abdominal distension (likely secondary to air swallowing)	gentamicin	23 mg once daily	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
769	**3 d**	**4.43**	**M**	**IP**	Mildly dilated ascending aorta, biventricular hypertrophy, laryngomalacia with laryngeal reflux	gentamicin	21 mg q2.5h	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
1024	**4 d**	**2.77**	**M**	**IP**	Trachoesophageal fistula repair, GORD	gentamicin	11.6 mg - first every 2 days then once daily	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
1148	**27 d**	**4.15**	**M**	**IP**	UTI	gentamicin	30 mg once daily	IV	IV	yes	no	OL	Dosage	MIMS: Children. Admin in 2-3 divided doses; Life threatening infection: initially 5-7.5 mg/kg/day
533	**15 y**		**M**	**OP**	Cold-induced vasculopathy of the digits	glyceryl trinitrate	2 mg/g prn	ointment	Topical	yes	no	OL	Age	MIMS: Safety and effectiveness of Rectogesic® (glyceryl trinitrate) in children and adolescents under 18 years of age have not been established. Not indicated for cold-induced vasculopathy.
612	**5 y**	**46.3**	**F**	**IP**	Precocious puberty	gonadorelin	100 mcg	IV	IV	no	no	UL	Formulation	Not registered in Australia.
671	**14 y**		**F**	**IP**	Short stature, obesity, obstructive sleep apnoea, nocturnal enuresis, acenthosis nigricans, pseudo-pseudohypoparathyroidism	gonadorelin	100 mcg	IV	IV	no	no	UL	Formulation	Not registered in Australia.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
156	4 y	20.55	M	IP	Swollen face, was urinating blood, decreased urine today, unwell. Asthmatic, recent tonsillitis. BP 150/90. Principal diagnosis: post streptococcal glomerulonephritis, pre-renal impairment, secondary hypertension, proteinuria	hydralazine	15mg bd	oral	PO	yes	no	OL	Age	MIMS: Safety and efficacy of hydralazine have not been established in children.
844	9 y		M	OP	Renal transplant, hypertension, epilepsy, chronic diarrhoea, metaphysical dysplasia	hydralazine	25 mg tds	liquid	PO	yes	no	OL	Age	MIMS: Safety and efficacy of hydralazine have not been established in children.
714	newborn	3.18	M	IP	Hypoxic ischaemic neonatal encephalopathy with mecorium aspiration and seizures	hydrocortisone	32mg QID	IV	IV	yes	no	OL	Age	TGA/ MIMS: No dose given for newborn infants - this child was born today. AMH 2008 also does not supply a dose for < 1 month old
1139	11 m	8.8	M	IP	Jejunal atresia, bowel obstruction, vomiting	hyoscine butylbromide	4 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: Dose for adults and children > 6 years: 20 - 40 mg. No dose for children < 6 years.
553	11 y		M	OP	Sickle cell disease, vitamin D deficiency	hydroxyurea	1d daily	oral	PO	yes	no	OL	Age	MIMS: Safety and efficacy have not been established in children
246	9 y	44.35	F	ED	Slipped femoral epiphysis. Pain on ambulation; there was obvious deformity and swelling.	ibuprofen	500mg single dose	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 5-10mg/kg 3 to 4 times per day.
246	9 y	44.35	F	ED	Slipped femoral epiphysis. Pain on ambulation; there was obvious deformity and swelling.	ibuprofen	500mg tds prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 5-10mg/kg 3 to 4 times per day.
257	1.5 y		F	ED	Cellulitis (MRSA); 12 hours of fever, vomit, rash to abdomen. Ringworm found around buttock	ibuprofen	150mg QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 5-10mg/kg 3 to 4 times per day.
944	1 y	8.68	F	IP	Bronchiolitis, LRTI	ibuprofen	100 mg tds prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 5-10mg/kg 3 to 4 times per day.
963	11 y		M	OP	Juvenile idiopathic arthritis	infliximab	250 mg 6 weekly	IV	IV	yes	no	OL	Indication	MIMS: Not registered for juvenile idiopathic arthritis
917	14 y		M	IP	Multiple sclerosis, exacerbation	interferon beta	62.5 mcg 3 weekly	IM	IM	yes	no	OL	Age	MIMS: Safety and effectiveness in those below 18 years of age have not been established in clinical trials.
272	4 y	16.9	M	ED	Viral pneumonitis (patient was pale, tachypnoeic and moderate intercostal muscle recession. (CXR showed no consolidation but bilateral infiltrates)	ipratropium	4 puffs - 3 doses every 20 min in ED	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
335	**7 y**		**F**	**ED**	Worsening asthma secondary to LRTI (Wheezing at home and appear cyanosed)	ipratropium	8 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
541	**1 y**		**M**	**ED**	Respiratory distress, vomiting	ipratropium	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
724	**8 y**		**M**	**IP**	Asthma exacerbation, viral	ipratropium	8 puffs thrice	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
750	**2 y**		**M**	**ED**	Asthma exacerbation, viral	ipratropium	4 puffs thrice	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1004	**2 y**	**13.76**	**M**	**ED**	Cough, asthma, URTI, viral illness	ipratropium	4 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1013	**5 y**		**F**	**IP**	Asthma exacerbation	ipratropium	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1026	**1 y 3 m**		**M**	**ED**	Asthma, viral wheeze	ipratropium	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1130	**5 y 5 m**		**F**	**IP**	Asthma (new onset)	ipratropium	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1132	**1 y 9 m**		**M**	**ED**	Asthma exacerbation	ipratropium	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1187	**6 y**		**F**	**ED**	Asthma, mild exacerbation	ipratropium	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff three times daily.
1193	**13 y**		**M**	**IP**	Asthma, allergic rhinitis, exacerbation	ipratropium	6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 6-12 yrs: 1 or 2 puff three to four times daily; < 6 yrs: 1 puff tds.
339	**1 y**	**9.6**	**M**	**ED**	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	ketamine	10 mg daily	IV	IV	yes	no	OL	Indication	Not indicated as analgesic. MIMS: Non-barbiturate IV and IM anaesthetic especially for short procedures; induction prior to other general anaesthetics; supplement to low potency agents.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
700	**2 y**		**F**	**OP**	Hyperinsulaemic hypoglyceamia of infancy, exocrine pancreatic insufficiency	lactulose	20 mg daily	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children (maintenance) < 12 months: 3-5 mL; 1-6 years: 5-10 mL; 7-14 years: 10 mL; daily.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	lactulose	15 ml bd prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children (maintenance) < 12 months: 3-5 mL; 1-6 years: 5-10 mL; 7-14 years: 10 mL; daily.
964	**12 y**		**M**	**OP**	Constipation, vitamin D deficient congestion	lactulose	25-30 ml	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Constipation adults: initially 15-30 mL daily until response (3 days) then 10-25 mL daily.
807	**7 m**	**5.26**	**F**	**IP**	CP, seizures and spasms, lissencephaly	lamotrigine	25 mg daily	tab	PO	yes	no	OL	Age	TGA: Lamotrigine is not recommended in children less than 2 years of age
554	**3 m**	**6.13**	**M**	**OP**	GORD	lansoprazole	15 mg daily	granules	PO	yes	no	OL	Age	MIMS: No dose for children < 1 year of age.
899	**2 m**		**F**	**IP**	GORD	lansoprazole	15 mg daily	granules	PO	yes	no	OL	Age	MIMS: No dose for children < 1 year of age.
333	**9 y**		**M**	**OP**	Traumatic mydriasis and scleral perforation. Had stick thrown in R eye.	latanoprost	1 drop night	eye drops	Eye drops	yes	no	OL	Age	MIMS: Xalatan® (latanoprost) is not recommended for use in children. Use in children has not been studied.
531	**4 y**		**F**	**OP**	Congenital glaucoma	latanoprost/ timolol (Xalacom®)	5/0.05mg/ml nocte BE	eye drop	Eye drops	yes	no	OL	Age	MIMS: Not recommended for use in children. Safety and effectiveness in children have not been established.
542	**11**		**F**	**ED**	Precocious puberty	leuprorelin acetate	22,5 mg	IM	IM	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established. Contraindicated in paediatrics.
884	**1 y 3 m**	**12.8**	**F**	**IP**	Hyponatraemia, seizures, left ventricular cyst (VP shunt), panhypothyroidism, diabetes insipidus, septo-optic dysplasia	levetiracetam	100 mg bd	liquid	PO	yes	no	OL	Age	MIMS: There are insufficient data to recommend the use of levetiracetam in children under 4 years of age.
1001	**2 y**		**M**	**OP**	Epilepsy, strabismus	levetiracetam	3 ml mane, 4 ml nocte; 100 mg/ml	liquid	PO	yes	no	OL	Age	MIMS: There are insufficient data to recommend the use of levetiracetam in children under 4 years of age.
1064	**3 y**	**15.15**	**M**	**IP**	Spinal fracture	lignocaine	40 mg	liquid	PO	yes	no	OL	ROA	Lignocaine IV solution was administered sublingually
725	**8 y**	**26.6**	**F**	**IP**	Chronic nephropathy	lisinopril	7.5 mg daily	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness of lisinopril in children have not been established
844	**9 y**		**M**	**OP**	Renal transplant, hypertension, epilepsy, chronic diarrhoea, metaphysical dysplasia	loperamide	2 mg tds	caps	PO	yes	no	OL	Age	MIMS: Imodium is contraindicated in children under the age of 12 years
146	**8 m**	**10.9**	**M**	**ED**	Viral illness (cough for 3 days, but no wheeze). Patients' PMH includes atopic dermatitis.	loratadine	2mg	oral	PO	yes	no	OL	Age	MIMS: No dosage given for children < 1 year. Claratyne Syrup (1 mg/mL): Children 2-12 years > 30kg: 10 mL daily; less than or equal to 30 kg: 5 mL daily. Children 1-2 years: 2.5 mL daily.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
903	**11 m**		**F**	**OP**	Eczema	loratadine	10 mg prn	liquid	PO	yes	no	OL	Age	MIMS: No dosage given for children < 1 year. Claratyne Syrup (1 mg/mL): Children 2-12 years > 30kg: 10 mL daily; less than or equal to 30 kg: 5 mL daily. Children 1-2 years: 2.5 mL daily.
945	**10 m**	**8.6**	**M**	**ED**	Impetigo	loratadine	2.5 mg daily	liquid	PO	yes	no	OL	Age	MIMS: No dosage given for children < 1 year. Claratyne Syrup (1 mg/mL): Children 2-12 years > 30kg: 10 mL daily; less than or equal to 30 kg: 5 mL daily. Children 1-2 years: 2.5 mL daily.
193	**14 y**	**42**	**F**	**IP**	Post-traumatic disorder. Showed depressive features and multi-sensory hallucinations.	lorazepam	05 - 1 mg daily PRN for severe agitation	oral	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
717	**13 y**	**46.85**	**M**	**IP**	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	lorazepam	1mg tds prn	oral	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	lorazepam	0.5 mg daily	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
804	**14 y**		**M**	**IP**	Burkitt's lymphoma	lorazepam	1 mg prn for nausea	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
1085	**11 y**		**M**	**ED**	Dysthemia, anxiety disorder, suicide attempt, hallucinations	lorazepam	0.5-1 mg tds prn	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
1177	**12 y**		**M**	**IP**	T-Cell ALL	lorazepam	1-2 mg bd prn	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
1197	**13 y**	**44.1**	**M**	**IP**	Nasopharyngeal carcinoma, PEG insertion	lorazepam	1-2 mg bd prn	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of lorazepam have not been established in children less than 16 years of age
725	**8 y**	**26.6**	**F**	**IP**	Chronic nephropathy	losartan	25 mg daily	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	magnesium chloride	5 ml/5 mmol	liquid	PO	no	no	UL	Formulation	PMH formulation
812	**6 y**	**25**	**F**	**IP**	Epilepsy, seizure with cyanotic episode, admitted after seen in ED; deceased 9/5/2010 (apnoea following LRTI and seizure)	melatonin	5 mg nocte	tab	PO	yes	no	OL	Age	TGA: Circadin® (melatonin) is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy
994	**2 d**	**2.04**	**M**	**IP**	Necrotising enterocolitis, short bowel syndrome	meropenem	42 mg bd	IV	IV	yes	no	OL	Age	MIMS: Efficacy and tolerability in infants under 3 months of age have not been established; therefore, meropenem is not recommended for use below this age

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
963	**11 y**		**F**	**OP**	Juvenile idiopathic arthritis	methotrexate	15 mg weekly	tab	PO	yes	no	OL	Indication	MIMS: Not registered for juvenile idiopathic arthritis
1177	**12 y**		**M**	**IP**	T-Cell ALL	methotrexate	5060 mg	IV	IV	yes	no	OL	Dosage	MIMS: Lymphoblastic leukaemia. Maintenance: 30 mg/m2 IMI twice wkly or 2.5 mg/kg IVI every 14 days
18	**5 y**	**30**		**IP**	Possible appendicitis (abdominal pain). Patient admitted for appendectomy	metoclopramide	4.5mg prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
399	**7 y**	**42.2**	**M**	**IP**	Myringotomy and insertion of grommets and adenoidectomy	metoclopramide	6mg QID prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
409	**7 y**	**32.45**	**M**	**IP**	Phimosis (elective admission). Patient was commenced on IV ondansetron 3mg QID prn.	metoclopramide	6mg tds	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
516	**2 y**	**9.6**	**M**	**OP**	Replantation of left thumb	metoclopramide	2mg tds	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
561	**12 y**			**IP**	Right gastroenemius release	metoclopramide	6 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
607	**8 y**	**20.6**	**M**	**IP**	Cerebral palsy, spasticity, is receiving BTX-A injection	metoclopramide	4 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
653	**7 y**	**29.8**	**M**	**IP**	Hemithyroidectomy	metoclopramide	6 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
678	**10 y**	**20**	**F**	**IP**	Adenotonsillectomy	metoclopramide	4 mg qid prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
761	**15 y**			**IP**	Spine injury, fracture L5 following MVA	metoclopramide	10 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
816	**9 y**			**IP**	Circumcision (phimosis), asthma	metoclopramide	4 mg qid prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
999	**8 y**	**39.65**		**IP**	Adenotonsillectomy	metoclopramide	8 mg prn	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
1095	**5 y**	**20.3**	**M**	**IP**	Left-sided cochlear implant, seasonal allergic rhinitis	metoclopramide	4 mg tds	IV	IV	yes	no	OL	Age	MIMS: In children and young adults < 20 years: restricted use to severe intractable vomiting of known cause, vomiting associated with radiation therapy or intolerance to cytotoxic drugs, assist in small bowel intubation.
725	**8 y**	**26.6**	**F**	**IP**	Chronic nephropathy	metolazone	5 mg alternate days	tab	PO	no	no	UL	Not registered	Not registered in Australia
446	**10 y**	**41.3**	**F**	**ED**	Appendectomy.	metronidazole	500mg - single dose	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children under 12 years: 8 hourly as for adults but the single IV dose is based on metronidazole 7.5mg/kg.
500	**11 y**	**47.2**	**M**	**ED**	Severe abdominal pain. Patient was diagnosed with acute appendicitis and underwent urgent appendectomy.	metronidazole	500mg	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children under 12 years: 8 hourly as for adults but the single IV dose is based on metronidazole 7.5mg/kg.
689	**27 d**	**3.31**	**F**	**IP**	Abdominal distension (likely secondary to air swallowing)	metronidazole	50mg once	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children under 12 years: 8 hourly as for adults but the single IV dose is based on metronidazole 7.5mg/kg.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
656	1 y 3 m		F	IP	Bronchiolitis	microlax	1 enema	enema	Rectal	yes	no	OL	Dosage	MIMS: Children < 3 yrs: insert 1/2 length of nozzle
1101	2 y	11.7	M	IP	Hydronephrosis, iron deficiency anaemia	microlax	1 enema	enema	Rectal	yes	no	OL	Dosage	MIMS: Children < 3 yrs: insert 1/2 length of nozzle
3	13 y	54.6	M	IP	Injury. Patient fell off a motor bike. Pain in the right clavicle and wrist, hit head but was wearing a helmet	midazolam	15mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
131	6 y		M	OP	Guillian Barre syndrome. PMH includes possible post viral neuropathy, post pituitary cyst, bronchiolitis and hyperactivity and vitamin D deficiency.	midazolam	5mg daily	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
262	7 m		F	IP	Possible parietal skull fracture - fell off the bed.	midazolam	2.4mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
339	1 y	9.6	M	ED	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	midazolam	1mg	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
361	4 y		M	ED	Foreign body in left nostril.	midazolam	7.5 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
456	11 y	24.5	M	IP	Neurological Symptoms - seizure/ fitting. Had seizure for 30 seconds which self resolved. Has recently been unwell with viral infection. Refusing oral intake. PMH of epilepsy, cerebral palsy, deafness, blindness	midazolam	5mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
485	1 y		M	OP	Review of coarction repair and duct litigation.	midazolam	11mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
591	17 y	75.2	M	IP	High risk T-cell ALL	midazolam	15 mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
601	11 y		M	IP	Cerebral palsy, mild spastic dysplegia, focal epilepsy (btx-injections)	midazolam	12 mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
607	8 y	20.6	M	IP	Cerebral palsy, spasticity.	midazolam	10 mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
646	**2 y**		**M**	**IP**	Brachial plexus injury	midazolam	8 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
683	**11 y**		**M**	**OP**	Idiopathic generalised epilepsy	midazolam	5 mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
690	**1 y**		**F**	**ED**	Generalised tonic clonic seizure, otitis media	midazolam	5 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
690	**1 y**		**F**	**ED**	Generalised tonic clonic seizure, otitis media	midazolam	3.5 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
692	**3 y**		**F**	**IP**	Repair of ostium premium defect and left AV valve regurgitation, small pericordial effusion.	midazolam	6 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
698	**3 y**		**M**	**IP**	Right orchidopexy testes	midazolam	10 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
714	**newborn**	**3.18**	**M**	**IP**	Hypoxic ischaemic neonatal encephalopathy with mecorium aspiration and seizures	midazolam	19 mg	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	midazolam	3 mg prn	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	midazolam	0.50 mg	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
797	**5 y**	**18.65**	**M**	**IP**	Allergic reaction	midazolam	4 mg	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
807	**7 m**	**5.26**	**F**	**IP**	Cerebral palsy, seizures and spasms, lissencephaly	midazolam	1.5 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
812	**6 y**	**25**	**F**	**IP**	Epilepsy, seizure with cyanotic episode, admitted after seen in ED; deceased 9/5/2010 (apnoea following LRTI and seizure)	midazolam	5 mg prn seizures	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
873	**2 y 6 m**	**16.05**	**M**	**IP**	Total colonic Hirschsprungs disease; closure of ileostomy	midazolam	8 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
876	**3 y**		**F**	**IP**	Right hip dysplasia, salter osteotomy with wound infection	midazolam	9 mg	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
920	**11 y**		**M**	**IP**	Cerebral palsy, right hemiparesis, GMFCS level 1	midazolam	10 mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
943	**3 y**		**M**	**ED**	Epileptic seizure, vomiting, febrile	midazolam	2.5 mg prn buccal for seizures	injection solution	Buccal	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
994	**2 d**	**2.04**	**M**	**IP**	Necrotising enterocolitis, short bowel syndrome	midazolam	200 mcg	IV	IV	yes	no	OL	Age	MIMS: Safety and effectiveness of midazolam in children below the age of 8 have not been established
1161	**15 y**	**60**	**F**	**OP**	Epilepsy	midazolam	10 mg prn	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
1177	**12 y**		**M**	**IP**	T-Cell ALL	midazolam	15 mg	injection solution	Buccal	yes	no	OL	ROA	MIMS: Midazolam is not available as an oral liquid - IV injection solution administered buccally.
73	**8 y**		**M**	**OP**	Alopecia areata. Eczema around eyes and elbows.	minoxidil	5% daily	topical	Topical	yes	no	OL	Age	MIMS: Safety and efficacy in patients under 18 years of age have not been established.
1175	**14 y**		**F**	**IP**	Paracetamol overdose	mirtazapine	15 mg nocte	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy of mirtazapine for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years have not been satisfactorily established
865	**3 m**	**7.21**	**M**	**ED**	Bronchiolitis (recurrent)	montelukast	2.5 mg daily 2/52	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in paediatric patients younger than 6 months of age have not been studied
91	**7 y**	**26**	**M**	**IP**	Acute appendicitis with perforation, admitted for laparoscopic appendectomy.	morphine	13mg	IV	IV	yes	no	OL	Dosage	MIMS: dose in children is 0.1-0.2mg/kg every four hours. 26 x 0.2 = 5.2mg - in this case dose was 13mg
390	**6 y**	**20**	**F**	**IP**	Adenotonsillectomy	morphine	25mg	IV	IV	yes	no	OL	Dosage	MIMS: Children - 0.05-0.1mg/kg slow IVI; 0.1-0.2mg/kg IM or SC. In this case greater than the 0.1mg/kg was administered IV
549	**1 y 8 m**	**17.4**	**M**	**IP**	Burns to face, chin, neck, chest, right arm (8% BSA), admitted for 18 days, skin graft	morphine	5-11mg q4h prn	oral	PO	yes	no	OL	Dosage	MIMS: Children: 0.1-0.2mg/kg every 4 hours (should be 1.74mg - 3.48mg)
625	**1 y 6 m**		**M**	**ED**	Viral illness, eczematous rash to face	mupirocin	20 mg/g	cream	Topical	yes	no	OL	Age	MIMS: The safety and efficacy of Bactroban cream has not been established in children less than 2 years of age
945	**10 m**	**8.6**	**M**	**ED**	Impetigo	mupirocin	20 mg/g tds 12/7	cream	Topical	yes	no	OL	Age	MIMS: The safety and efficacy of Bactroban cream has not been established in children less than 2 years of age
917	**14 y**		**M**	**IP**	Multiple sclerosis, exacerbation	natalizumab	300 mg monthly	IV	IV	yes	no	OL	Age	MIMS: Tysabri® (natalizumab) is not indicated for use in paediatric and adolescent patients less than 18 years

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
156	**4 y**	**20.55**	**M**	**IP**	Swollen face, was urinating blood, decreased urine today, unwell. Asthmatic, recent tonsillitis. BP 150/90. Principal diagnosis: post streptococcal glomerulonephritis, pre-renal impairment, secondary hypertension, proteinuria	nifedipine	2.5mg prn	oral	PO	yes	no	OL	Age	MIMS: Does not specify a paediatric dose. TGA: The safety and efficacy of ADALAT in children below 18 years has not been established
533	**15 y**		**M**	**OP**	Cold-induced vasculopathy of the digits	nifedipine	5 mg daily	tab	PO	yes	no	OL	Age	TGA: The safety and efficacy of ADALAT in children below 18 years has not been established; not indicated for cold-induced vasculopathy
1161	**15 y**	**60**	**F**	**OP**	Epilepsy	nitrazepam	7.5 mg bd, 10 mg nocte	tab	PO	yes	no	OL	Indication	MIMS: only indicated for insomnia
700	**2 y**		**F**	**OP**	Hyperinsulaemic hypoglyceamia of infancy, exocrine pancreatic insufficiency	octreotide	10 mg 3 weekly	IV	IV	yes	no	OL	Age	MIMS: Experience with octreotide in children is very limited.
283	**3 y**		**M**	**OP**	HSV ulceration of the cornea. Pain/sensitive to light - patient treated for blepharitis for many months.	ofloxacin	1 drop QID	gutt	Eye drops	yes	no	OL	Age	MIMS: Adequate clinical studies of the safety of topical ophthalmic treatment with ofloxacin have not been conducted. Ocuflox should be avoided in children who have not attained joint maturity.
962	**2 y**	**17.65**	**M**	**IP**	Cystic swelling to neck, infective exacerbation	picibanil	9 ml/1 U	IM	IM	no	no	UL	SAS	Not registered in Australia
815	**10 y**		**F**	**ED**	Autistic disorder, severe behavioural disturbance	olanzapine	5 mg prn	tab (wafer)	PO	yes	no	OL	Age	MIMS: Zyprexa has not been studied in patients under 18 years of age
1036	**12 y**	**60**	**M**	**ED**	Chemical intoxication (vodka, cologne)	olanzapine	5 mg	tab (wafer)	PO	yes	no	OL	Age	MIMS: Zyprexa has not been studied in patients under 18 years of age
112	**4 m**	**4.58**	**F**	**ED**	Feeding difficulties. PMH includes GORD, constipation and poor weight gain.	omeprazole	10mg tds	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
151	**1 m**	**3.47**	**F**	**ED**	Gastro-oesophageal reflux disorder. Patient was commenced on omeprazole 2.5mg daily for 2 months.	omeprazole	2.5mg daily	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
538	**1 y 3 m**	**8.22**	**F**	**OP**	Gastric reflux, feeding difficulties	omeprazole	8 mg bd	tab (dispersed)	PO	yes	no	OL	Dosage	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
626	**8 m**	**9.91**	**M**	**OP**	Benign macrocephaly, recurrent vomiting, recurrent cough	omeprazole	10 mg	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
768	**3 m**	**6.05**	**F**	**IP**	Bronchiolitis, RS Virus detected	omeprazole	5 mg nocte	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
769	**3 d**	**4.43**	**M**	**IP**	Mildly dilated ascending aorta, biventricular hypertrophy, laryngomalacia with laryngeal reflux	omeprazole	5 mg daily	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
862	**7 m**	**9.9**	**M**	**IP**	Vomiting, fever, irritability,	omeprazole	6 mg bd via PEG	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
994	**2 d**	**2.04**	**M**	**IP**	Necrotising enterocolitis, short bowel syndrome	omeprazole	5 mg daily	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
1020	**2 w**		**F**	**ED**	Unsettled, silent reflux?	omeprazole	5 mg daily	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
1112	**8 m**	**5.34**	**M**	**ED**	Bronchiolitis	omeprazole	2.5 mg (1/4 tab)	tab (dispersed)	PO	yes	no	OL	Age	MIMS: For children weighing 10 to 20 kg the recommended dose is Losec Tablets 10 mg once daily; this child weighs less than 10 kg and is on a bd regime. No dosage given for children < 1 year
3	**13 y**	**54.6**	**M**	**IP**	Injury. Patient fell off a motor bike. Pain in the right clavicle and wrist, hit head but was wearing a helmet	ondansetron	4mg QID prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
18	**5 y**	**30**	**F**	**IP**	Possible appendicitis (abdominal pain). Patient admitted for appendectomy	ondansetron	3mg six hourly	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
70	**9 y**		**M**	**IP**	Fractured forearm	ondansetron	3mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
88	**1 y**	**11.4**	**F**	**ED**	Injury. Left upper limb. (patient was admitted for exploration and repair)	ondansetron	2mg PONV	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established
91	**7 y**	**26**	**M**	**IP**	Acute appendicitis with perforation, admitted for laparoscopic appendectomy.	ondansetron	2mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
100	**8 y**	**27.82**	**F**	**IP**	Left supracondylar fracture	ondansetron	2.7mg q6h prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
106	**11 y**	**35**	**F**	**ED**	Appendicitis. (Patient underwent laparoscopic appendectomy)	ondansetron	4mg TDS prn postoperatively	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
120	**12 y**	**51.9**	**M**	**IP**	Removal of plate and screws from previous left radius fracture	ondansetron	4mg tds prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
161	**3 y**	**15**	**M**	**ED**	Facial lip laceration (patient admitted, wound was cleaned and sutured)	ondansetron	2mg q6h	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
163	**7 y**	**26.65**	**M**	**IP**	Burn to left upper thigh and dorsal penis from hot noodles. (mild difficulties voiding, mild discomfort)	ondansetron	4mg tds prn	oral liquid		yes	no	OL	Indication	MIMS: Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting
207	**17 y**	**16.6**	**F**	**IP**	Lipomeningocele-sacrum region. (Liposuction lumbar-sacral region, surgery complicated by drainage and there were some concerns that this may have been CSF)	ondansetron	4mg q6h prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
208	**17 y**	**65**	**F**	**IP**	Dental extraction and restoration	ondansetron	4mg qid	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
209	**16 y**		**M**	**IP**	Tonsillectomy and cautery of turbinates	ondansetron	8mg tds prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
253	**2 y**	**13.05**	**M**	**IP**	Dental abscess. Admitted for dental extraction under general anaesthesia	ondansetron	1mg every 6 hrs	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
316	**12 y**	**34.25**	**M**	**ED**	Acute appendicitis (Patient admitted and underwent laparoscopic appendectomy)	ondansetron	4mg bd	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
332	**3 y**	**16.05**	**M**	**OP**	Injury. Right upper limb and thumb fractured	ondansetron	1.5mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
358	**6 y**	**26.45**	**M**	**ED**	Injury - closed fracture	ondansetron	3mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
390	**6 y**	**20**	**F**	**IP**	Adenotonsillectomy	ondansetron	2mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
399	**7 y**	**42.2**	**M**	**IP**	Myringotomy and insertion of grommets and adenoidectomy	ondansetron	3mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
409	**7 y**	**32.45**	**M**	**IP**	Phimosis (elective admission). Patient was commenced on IV ondansetron 3mg QID prn.	ondansetron	3mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
414	**7 y**	**47.85**	**M**	**ED**	Appendicitis. Patient was admitted for laparoscopic appendectomy.	ondansetron	4mg eight hrly prn	oral liquid		yes	no	OL	Indication	MIMS: Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting.
458	**9 y**	**37.3**	**F**	**IP**	Tonsillectomy	ondansetron	3.7mg q6h	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
476	**4 m**		**M**	**IP**	Posterior encephalocele (Patient admitted for MRI of brain and spine under GA)	ondansetron	1mg QID prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established
493	**3 y**		**M**	**IP**	Follow-up of MRI to assess progress of left cerebral lesion. (Acute onset left sided squint July 2008, patient noted to be clumsy). CT performed and showed mild abnormality of left hemisphere.	ondansetron	4mg 8 hrly	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
498	**16 y**		**M**	**IP**	Hodgkin Lymphoma (diagnosed in 2006)	ondansetron	8mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
500	**11 y**	**47.2**	**M**	**ED**	Severe abdominal pain. Patient was diagnosed with acute appendicitis and underwent urgent appendectomy.	ondansetron	7mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
516	**2 y**	**9.6**	**M**	**OP**	Replantation of left thumb	ondansetron	1mg IV QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
523	**1 y**		**M**	**IP**	Subcoronal hypospadias repair	ondansetron	1mg QID	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
528	**5 y**	**26.3**	**F**	**IP**	Biopsy scalp lesion, right forearm lesion	ondansetron	2.6mg tds	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
549	**1 y 8 m**	**17.4**	**M**	**IP**	Burns to face, chin, neck, chest, right arm (8% BSA), admitted for 18 days, skin graft	ondansetron	1.5 mg tds prn	liquid	PO	yes	no	OL	Age	MIMS: Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting. The clinical safety of ondansetron in children under 2 years has not been established.
561	**12 y**		**M**	**IP**	Right gastroenemius release	ondansetron	4 mg qid prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
571	**8 y**	**25.8**	**F**	**ED**	Facial laceration	ondansetron	2.5mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
572	**11 y**	**47.2**	**M**	**IP**	Excision of congenital melanocytic nevus on left posterior thigh	ondansetron	4mg bd	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
577	**11 y**	**35.8**	**M**	**IP**	Irritable bowel syndrome, constipation, weight loss	ondansetron	3mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
587	**6 y**	**20.7**	**F**	**ED**	Right-sided pneumonia with pleural effusion	ondansetron	3mg every 8 hrs prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
593	**15 y**		**M**	**IP**	Crohn's disease	ondansetron	4mg QID prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
643	**9 y**	**33.7**	**F**	**IP**	Diabetes Mellitus type 1, hypoglycaemia	ondansetron	4 mg tds prn	liquid		yes	no	OL	Indication	MIMS: Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting. The clinical safety of ondansetron in children under 2 years has not been established.
652	**4 y**	**19.85**	**M**	**IP**	Dental trauma, extraction	ondansetron	2mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
653	**7 y**	**29.8**	**M**	**IP**	Hemithyroidectomy	ondansetron	3mg q4h prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
676	**10 y**		**M**	**IP**	Admitted for abdominal pain - colonoscopy, endoscopy, laparotomy, ceacal adhesion	ondansetron	2mg bd prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
678	**10 y**	**20**	**F**	**IP**	Adenotonsillectomy	ondansetron	2.5 mg tds prn	liquid		yes	no	OL	Indication	MIMS: Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting. The clinical safety of ondansetron in children under 2 years has not been established.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
679	**11 y**	**40.05**	**F**	**IP**	Diabetes Mellitus type I, hypoglycaemic seizure	ondansetron	4mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
684	**1 y 2 m**		**F**	**IP**	Recurrent OM and insertion grommets	ondansetron	1 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
687	**3 y**		**F**	**IP**	Adenotonsillectomy	ondansetron	2mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
695	**2 y**		**F**	**IP**	Bilateral esotropia	ondansetron	2mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
703	**13 y**		**M**	**IP**	Laceration to perianal area, wound infection	ondansetron	4mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
706	**10 y**		**F**	**IP**	Adenotonsillectomy	ondansetron	4mg tds	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
717	**13 y**	**46.85**	**M**	**IP**	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	ondansetron	6mg tds prn	IV	IV	yes	no	OL	Dosage	For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, a single dose of 8 mg should be administered by injection. To protect against delayed emesis after the first 24 hours, ondansetron should be continued orally at a dosage of 8 mg twice daily for up to five days.

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720	**10 y**	**44.1**	**M**	**IP**	Right testicular hydratid torsion	ondansetron	4mg QID prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
740	**1 y 8 m**	**10.35**	**M**	**IP**	Insertion of grommets	ondansetron	1,5 mg qid prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
749	**2 y**	**12.55**	**M**	**ED**	Split lower lip, croup	ondansetron	2 mg qid	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
754	**11 y**	**39.3**	**M**	**IP**	Injury to big toe, stubbed, swelling not improving	ondansetron	4 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
761	**15 y**		**M**	**IP**	Spine injury, fracture L5 following MVA	ondansetron	8 mg tds prn	tab (wafer)	PO	yes	no	OL	Indication	MIMS: Ondansetron wafers are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting
761	**15 y**		**M**	**IP**	Spine injury, fracture L5 following MVA	ondansetron	4 mg tds prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
779	**17 y**		**M**	**IP**	Correction of anterior open bite	ondansetron	4 mg tds prn	tab (wafer)	PO	yes	no	OL	Indication	MIMS: Ondansetron wafers are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting

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786	**13 y**		**M**	**ED**	Appendicitis	ondansetron	4mg qid prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
793	**9 y**		**M**	**IP**	Right torted hydatid of Morgagni excision	ondansetron	4 mg tds	tab (wafer)	PO	yes	no	OL	Indication	MIMS: Ondansetron wafers are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting
793	**9 y**		**M**	**IP**	Right torted hydatid of Morgagni excision	ondansetron	4 mg qid	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
816	**9 y**		**M**	**IP**	Circumcision (phimosis), asthma	ondansetron	6 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
818	**2 y**	**15.7**	**F**	**ED**	Foreign body left nostril, removed under GA	ondansetron	2 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
830	**8 y**	**28.6**	**M**	**IP**	Esotropia, squint repair	ondansetron	3 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
831	**10 y**	**38.4**	**F**	**IP**	Chronic recurrent multifocal osteomyelitis, pain management	ondansetron	4 mg prn 1/12	tab (wafer)	PO	yes	no	OL	Indication	MIMS: Ondansetron wafers are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
832	**12 y**	**43**	**F**	**IP**	Intrinsic brain stem glioma; deceased 17.12.08	ondansetron	8 mg tds	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
836	**16 y**		**M**	**IP**	Orbital floor fracture, eye trauma, dizzy, nausea	ondansetron	8 mg	tab (wafer)	PO	yes	no	OL	Indication	MIMS: Ondansetron wafers are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting
843	**10 y**		**M**	**IP**	Spastic quadriplegia, test for intrathecal baclofen	ondansetron	2 mg tds	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
862	**7 m**	**9.9**	**M**	**IP**	Vomiting, fever, irritability,	ondansetron	0.5 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
892	**8 y**	**26.2**	**M**	**IP**	Constipation: ACE-procedure, appendectomy	ondansetron	4 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
904	**6 y**	**22.95**	**M**	**IP**	Burn to left foot, skin grafts	ondansetron	2.5 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
907	**3 m**	**4.59**	**F**	**IP**	Bilateral inguinal hernia repair	ondansetron	0.5 mg qid	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.

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913	**14 y**	**45.2**	**F**	**IP**	Excision of granulated tissue right nostril	ondansetron	4 mg qid prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
915	**16 y**		**M**	**OP**	Single dysplastic kidney, renal failure, dialysis. Abdominal pain after dialysis.	ondansetron	4 mg	tab	PO	yes	no	OL	Indication	MIMS: Ondansetron tablets are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting.
922	**10 y**	**39.1**	**F**	**IP**	Fracture left forearm	ondansetron	4 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
923	**15 y**		**F**	**IP**	Spondylo-epiphyseal dysplasia tarda pseaudorheumatoid arthritis; scoliosis, spinal fusion	ondansetron	3 mg tds prn	tab (wafer)		yes	no	OL	Indication	MIMS: Ondansetron wafers are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting.
924	**10 y**	**33.5**	**F**	**ED**	Throat infection, vomiting, post-op	ondansetron	4 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
947	**4 y**	**14.55**	**M**	**IP**	Persistent neck lesion, excision	ondansetron	1.5 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
958	**5 y**	**17**	**M**	**ED**	Head injury, laceration of forehead	ondansetron	2 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	ondansetron	8 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
962	**2 y**	**17.65**	**M**	**IP**	Cystic swelling to neck, infective exacerbation	ondansetron	2 mg qid prn	liquid	PO	yes	no	OL	Age	Off-label for age and indication. MIMS states "Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting in children > 4 years".
974	**10 y**	**37.09**	**F**	**IP**	Excision of nose lesion and polydactyl left 5th toe	ondansetron	4 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
988	**3 y**	**14.35**	**F**	**IP**	Facial laceration, sutured	ondansetron	1.5 mg tds prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
1003	**12 y**	**41.45**	**M**	**IP**	Residual left central perforation (repair), right pinhole perforation	ondansetron	4 mg qid prn	IV	IV	yes	no	OL	Dosage	Greater dose frequency than stated in MIMS: For prevention of postoperative nausea and vomiting in adults, a single dose of 4mg may be administered by injection at induction of anaesthesia. For treatment of established postoperative nausea and vomiting, a single dose of 4 mg by injection is recommended and if necessary, the dose may be increased to 8 mg.
1008	**1 y**		**M**	**IP**	Removal of duplicated left thumb	ondansetron	1 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
1029	**3 y**	**17.2**	**M**	**IP**	Foreign body in nose	ondansetron	2 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1057	**2 y**	**14.1**	**M**	**IP**	Dental trauma, extraction	ondansetron	1.5 mg qid	liquid	PO	yes	no	OL	Age	Off-label for age and indication. MIMS states "Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting in children > 4 years".
1064	**3 y**	**15.15**	**M**	**IP**	Spinal fracture	ondansetron	2 mg tds	tab	PO	yes	no	OL	Age	Off-label for age and indication. MIMS states "Ondansetron syrup is only licensed for cytotoxic chemo/radiotherapy induced nausea and vomiting in children > 4 years".
1068	**4 y**	**17.2**	**M**	**IP**	Upper lip laceration, admitted after ED	ondansetron	2 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
1095	**5 y**	**20.3**	**M**	**IP**	Left-sided cochlear implant, seasonal allergic rhinitis	ondansetron	2 mg qid	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
1105	**1 y 8 m**	**13.7**	**M**	**IP**	Right 4th nerve palsy, Oblique myectomy	ondansetron	1.5 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
1110	**5 m**	**5.11**	**F**	**IP**	Bilateral hernias, right ovary and fallopial tube prolapse	ondansetron	0.5 mg qid prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
1116	**3 m**	**4.84**	**F**	**IP**	Cleft lip repair	ondansetron	0.5 mg tds prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.
1162	**15 y**	**106**	**M**	**IP**	Right hip injury, removal of screw	ondansetron	4 mg tds prn	tab	PO	yes	no	OL	Indication	MIMS: Ondansetron tablets are only licensed for cytotoxic chemotherapy and radiotherapy induced nausea and vomiting.
1166	**8 y**	**29.4**	**M**	**IP**	Right post septal abscess secondary to sinogesic source (nose)	ondansetron	3 mg qid prn	IV	IV	yes	no	OL	Dosage	More than one dose per day. MIMS states: " Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment".
1175	**14 y**		**F**	**IP**	Paracetamol overdose	ondansetron	4 - 8 mg bd prn	IV	IV	yes	no	OL	Indication	MIMS: Indicated for nausea and vomiting induced by cytotoxic therapy and radiotherapy; prevention & treatment of PONV.
1199	**1 y 10 m**	**11.9**	**M**	**IP**	Neck abscess, drainage	ondansetron	1.5 mg qid prn	IV	IV	yes	no	OL	Age	MIMS: The clinical safety of ondansetron in children under 2 years has not been established.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1101	**2 y**	**11.7**	**M**	**IP**	Hydronephrosis, iron deficiency anaemia	oxybutynin	2 mg tds	tab	PO	yes	no	OL	Age	MIMS: As there is insufficient clinical data for children under age 5, Ditropan is not recommended for this age group.
18	**5 y**	**30**	**F**	**IP**	Possible appendicitis (abdominal pain). Patient admitted for appendectomy	oxycodone	5mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
46	**7 y**	**20.9**	**F**	**IP**	Possible appendicitis and mild dehydration.	oxycodone	2-4mg q4h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
91	**7 y**	**26**	**M**	**IP**	Acute appendicitis with perforation, admitted for laparoscopic appendectomy.	oxycodone	3mg QID prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
106	**11 y**	**35**	**F**	**ED**	Appendicitis. (Patient underwent laparoscopic appendectomy)	oxycodone	3.5-7mg QID prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
132	**5 y**	**18.2**	**F**	**IP**	Adenotonsillectomy	oxycodone	3mg every 4 hrs prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
205	**5 y**	**19.75**	**M**	**IP**	Adenoidectomy and cautery of turbinates	oxycodone	3-6mg every 4 hrs prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
219	**10 y**	**44**	**M**	**IP**	Adenoidectomy without tonsillectomy and cauterisation of nasal turbinates.	oxycodone	4mg QID prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
246	**9 y**	**44.35**	**F**	**ED**	Slipped femoral epiphysis (pain on ambulation and there was obvious deformity and swelling, patient was admitted for hip pinning)	oxycodone IR	5mg q4h prn	tabs	PO	yes	no	OL	Age	MIMS: Oxycodone tablets: should not be administered to children.
316	**12 y**	**34.25**	**M**	**ED**	Acute appendicitis (Patient admitted and underwent laparoscopic appendectomy)	oxycodone	3.5-7mg q3h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
399	**7 y**	**42.2**	**M**	**IP**	Myringotomy and insertion of grommets and adenoidectomy	oxycodone	3-6mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
414	**7 y**	**47.85**	**M**	**ED**	Appendicitis. Patient was admitted for laparoscopic appendectomy.	oxycodone	5mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
446	**10 y**	**41.3**	**F**	**ED**	Appendectomy.	oxycodone	4-6mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
458	**9 y**	**37.3**	**F**	**IP**	Tonsillectomy	oxycodone	3.7 mg tds prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
498	**16 y**		**M**	**IP**	Hodgkin Lymphoma (diagnosed in 2006)	oxycodone (OxyNorm®)	5mL q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
500	**11 y**	**47.2**	**M**	**ED**	Severe abdominal pain. Patient was diagnosed with acute appendicitis and underwent urgent appendectomy.	oxycodone (Endone®)	5mg q4h	tabs	PO	yes	no	OL	Age	MIMS: Oxycodone tablets: should not be administered to children.
600	**12 y**		**F**	**IP**	Patello femoral ligament reconstruction, cerebral palsy, epilepsy	oxycodone	5 mg qid prn	caps	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
602	**10 y**		**F**	**ED**	Abdominal pain, central, radiating to back	oxycodone	5 mg	tabs	PO	yes	no	OL	Age	MIMS: Oxycodone tablets: should not be administered to children.
605	**8 y**	**34.5**	**F**	**IP**	Cellulitis to ear	oxycodone	3-6 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
650	**2 y**		**M**	**IP**	Shunted hydrocephalus (blocked shunt), epilepsy, congenital aquaductal stenosis	oxycodone	1 mg	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
653	**7 y**	**29.8**	**M**	**IP**	Hemithyroidectomy	oxycodone	3-5 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
676	**10 y**		**M**	**IP**	Admitted for abdominal pain - colonoscopy, endoscopy, laparotomy, ceacal adhesion	oxycodone	2-4 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
678	**10 y**	**20**	**F**	**IP**	Adenotonsillectomy	oxycodone	1.9 mg tds prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
706	**10 y**		**F**	**IP**	Adenotonsillectomy	oxycodone	3.8 mg	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
720	**10 y**	**44.1**	**M**	**IP**	Right testicular hydratid torsion	oxycodone	4-6mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	oxycodone	5mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	oxycodone	0.5 mg q3-4 h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
754	**11 y**	**39.3**	**M**	**IP**	Injury to big toe, stubbed, swelling not improving	oxycodone	4-8 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
762	**10 m**	**6.72**	**F**	**IP**	Bilateral open hip surgery	oxycodone	0.5 mg q4-6h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
830	**8 y**	**28.6**	**M**	**IP**	Esotropia, squint repair	oxycodone	3 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
831	**10 y**	**38.4**	**F**	**IP**	Chronic recurrent multifocal osteomyelitis, pain management	oxycodone	3-8 mg	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
832	**12 y**	**43**	**F**	**IP**	Intrinsic brain stem glioma; deceased 17.12.08	oxycodone	5 mg qid prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
873	**2 y 6 m**	**16.05**	**M**	**IP**	Total colonic Hirschsprungs disease; closure of ileostomy	oxycodone	1 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
876	**3 y**		**F**	**IP**	Right hip dysplasia, salter osteotomy with wound infection	oxycodone	1.8 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
886	**3 y**		**M**	**IP**	Adenotonsillectomy	oxycodone	1.5 mg q4h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
892	**8 y**	**26.2**	**M**	**IP**	Constipation: ACE-procedure, appendectomy	oxycodone	2-5 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
904	**6 y**	**22.95**	**M**	**IP**	Burn to left foot, skin grafts	oxycodone	4 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
924	**10 y**	**33.5**	**F**	**ED**	Throat infection, vomiting, post-op	oxycodone	4 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
926	**11 y**		**M**	**ED**	Fracture distal radius and ulna	oxycodone	5-10 mg q4h	tabs	PO	yes	no	OL	Age	MIMS: Oxycodone tablets: should not be administered to children.
962	**2 y**	**17.65**	**M**	**IP**	Cystic swelling to neck, infective exacerbation	oxycodone	2 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
999	**8 y**	**39.65**	**F**	**IP**	Adenotonsillectomy	oxycodone	3.5 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1003	**12 y**	**41.45**	**M**	**IP**	Residual left central perforation (repair), right pinhole perforation	oxycodone	4-8 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1008	**1 y**		**M**	**IP**	Removal of duplicated left thumb	oxycodone	1 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1015	**7 y**		**F**	**IP**	Hearing loss, left cholesteatoma	oxycodone	2-4 mg q4h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1025	**5 y**		**F**	**IP**	Right tibia, low trauma fracture, skin lesions	oxycodone	2.20 mg qid prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1029	**3 y**	**17.2**	**M**	**IP**	Foreign body in nose	oxycodone	1.5-2 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1083	**11 y**	**38**	**M**	**IP**	Laceration to lower leg	oxycodone	2.5 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1100	**4 y**	**17.15**	**M**	**IP**	Supracondylar elbow fracture	oxycodone	3 mg	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1166	**8 y**	**29.4**	**M**	**IP**	Right post septal abscess secondary to sinogesic source (nose)	oxycodone	3-6 mg q4h prn	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
1199	**1 y 10 m**	**11.9**	**M**	**IP**	Neck abscess, drainage	oxycodone	1.5 mg q4h	oral liquid	PO	yes	no	OL	Age	MIMS: Oxycodone capsules, liquid and injection should not be used in patients under 18 years of age.
18	**5 y**	**30**	**F**	**IP**	Appendectomy	Painstop Day®	16mL six hourly prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
21	**2 y**		**F**	**ED**	Inflamed/infected little finger	Painstop Day®	8mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
46	**7 y**	**20.9**	**F**	**IP**	Possible appendicitis and mild dehydration.	Painstop Day®	16mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
70	**9 y**		**M**	**IP**	Fractured forearm	Painstop Day®	24 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
88	**1 y**	**11.4**	**F**	**ED**	Injury. Left upper limb. (patient was admitted for exploration and repair)	Painstop Day®	6.5 mL orally 4-6 hourly	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
100	**8 y**	**27.82**	**F**	**IP**	Left supracondylar fracture	Painstop Day®	20mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
106	**11 y**	**35**	**F**	**ED**	Appendicitis. (Patient underwent laparoscopic appendectomy)	Painstop Day®	28mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
118	**11 y**		**F**	**OP**	Mild lid oedema and mild generalized conjunctiva infection.	Painstop Day®	30mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
127	**8 y**	**42.9**	**M**	**ED**	Infection/inflammation of little toe - swelling, and boil like lesions on the inner aspects of leg-thigh.	Painstop Day®	30 mL (one dose in ED)	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
130	**6 y**	**30**	**F**	**ED**	Gradual onset of ear pain but no discharge; itchy ear, throat sl red; possible otitis externa.	Painstop Day®	24mL - one dose in ED	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
132	**5 y**	**18.2**	**F**	**IP**	Adenotonsillectomy	Painstop Day®	14mL every 6 hrs when needed	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
163	**7 y**	**26.65**	**M**	**IP**	Burn to left upper thigh and dorsal penis from hot noodles. (patient had mild difficulties voiding and was in mild discomfort)	Painstop Day®	21mL q6h prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
181	**7 y**	**26.25**	**M**	**IP**	Fractured radius and ulna following a fall at school. Obvious deformity observed	Painstop Day®	21mL (1 dose)	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
221	**3 y**	**13.6**	**M**	**ED**	Lacerated right little toe and had febrile convulsion and otitis media	Painstop Day®	10.5 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
246	**9 y**	**44.35**	**F**	**ED**	Slipped femoral epiphysis (pain on ambulation and there was obvious deformity and swelling, patient was admitted for hip pinning)	Painstop Day®	35mL - one dose in ED	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
257	**1.5 y**		**F**	**ED**	Cellulitis (MRSA); 12 hours of fever, vomit, rash to abdomen. Ringworm found around buttock	Painstop Day®	11.8 mL six hourly	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
327	**6 y**	**19**	**F**	**ED**	Herpes stomatitis (multiple mouth ulcers on lips and tongue)	Painstop Day®	15mL - one dose in ED	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
358	**6 y**	**26.45**	**M**	**ED**	Injury - closed fracture	Painstop Day®	20mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
390	**6 y**	**20**	**F**	**IP**	Adenotonsillectomy	Painstop Day®	16 mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
400	**8 y**	**34.85**	**F**	**IP**	Patient complained of severe abdominal pain and was admitted (in-patient) for overnight observation.	Painstop Day®	27mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
402	**7 y**	**29.75**	**M**	**IP**	Bilateral scrotal exploration for excision of hydatid.	Painstop Day®	23mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
434	**1 y**	**10.16**	**M**	**ED**	URTI and otitis media (Cough, blocked nose and head tilted towards ear that's paining and fever)	Painstop Day®	8mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
452	**9 y**		**M**	**IP**	Possible vasculitis (Patient admitted for investigation and treatment of possible polyarteritis nodosum)	Painstop Day®	25mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
474	**4 y**	**16.9**	**M**	**ED**	Balanitis (inflammation of glans penis) - difficulty voiding and also suffered pain while micturating. It then progressed to inability to pass urine	Painstop Day®	14mL - one dose in ED	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
490	**1 y**		**F**	**IP**	Left 2nd toe doctylitis. Aspiration and injection of left 2nd toe.	Painstop Day®	7mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
503	**10 y**	**33.8**	**F**	**IP**	Abdominal pain, possible appendicitis	Painstop Day®	26mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
528	**5 y**	**26.3**	**F**	**IP**	Biopsy scalp lesion, right forearm lesion	Painstop Day®	20mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
539	**1 y**	**10.5**	**M**	**OP**	Head injury, bruise to face and graze to head	Painstop Day®	8 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
549	**1 y 8 m**	**17.4**	**M**	**IP**	Burns to face, chin, neck, chest, right arm (8% BSA), admitted for 18 days, skin graft	Painstop Day®	8 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
552	**9 y**	**26.9**	**F**	**OP**	Fracture left upper thumb, seen in ED at 08.08.08	Painstop Day®	16 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
568	**11 y**	**41**	**F**	**ED**	Central abdominal pain	Painstop Day®	32mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
571	**8 y**	**25.8**	**F**	**ED**	Facial laceration	Painstop Day®	20 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
580	**7 y**	**27.2**	**M**	**ED**	Post-tonsillectomy, woke with blood around mouth and over sheets	Painstop Day®	20mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
586	**6 y**		**F**	**ED**	Injury-Left upper limb burnt because of a car cigarette lighter 10 minutes earlier. Placed in cold water at triage	Painstop Day®	16 mL	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
587	**6 y**	**20.7**	**F**	**ED**	Right-sided pneumonia with pleural effusion	Painstop Day®	16mL q6h prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
605	**8 y**	**34.5**	**F**	**IP**	Cellulitis to ear	Painstop Day®	27.5mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
639	**5 y**	**22.5**	**M**	**ED**	Central abdominal pain, pain to shoulders	Painstop Day®	18mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
676	**10 y**		**M**	**IP**	Admitted for abdominal pain - colonoscopy, endoscopy, laparotomy, ceacal adhesion	Painstop Day®	18mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
688	**6y**		**M**	**OP**	Fractured arm	Painstop Day®	16mL q6h prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
691	**3 y**	**16.4**	**M**	**IP**	Laceration to lip	Painstop Day®	12mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
695	**2 y**		**F**	**IP**	Bilateral esotropia	Painstop Day®	12mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
698	**3 y**		**M**	**IP**	Right orchidopexy testes	Painstop Day®	12mL QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
749	**2 y**	**12.55**	**M**	**ED**	Split lower lip, croup	Painstop Day®	9 mL qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
765	**2 y**	**18**	**M**	**ED**	Muscular injury to neck	Painstop Day®	14.5 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
792	**8 y**	**25.05**	**F**	**ED**	Bilateral eye problem, swelling and redness, allergic reaction	Painstop Day®	20 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
793	**9 y**		**M**	**IP**	Right torted hydatid of Morgagni excision	Painstop Day®	30 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
831	**10 y**	**38.4**	**F**	**IP**	Chronic recurrent multifocal osteomyelitis, pain management	Painstop Day®	30 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
833	**8 y**	**22.8**	**M**	**IP**	Mosaic down syndrome, left tibial osteotomy and fibular epiphyseodesis, constipation	Painstop Day®	18 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
922	**10 y**	**39.1**	**F**	**IP**	Fracture left forearm	Painstop Day®	32 mL q4h	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
924	**10 y**	**33.5**	**F**	**ED**	Throat infection, vomiting, post-op	Painstop Day®	25 mL tds 5/7	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
933	**5 y**	**20**	**M**	**IP**	Mastoiditis, grommets placed	Painstop Day®	16 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
969	**4 y**	**30.4**	**M**	**ED**	Painful left hip/thigh	Painstop Day®	12 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
975	**10 y**		**M**	**IP**	Foreskin adhesion, asthma, rhinitis	Painstop Day®	18 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
988	**3 y**	**14.35**	**F**	**IP**	Facial laceration, sutured	Painstop Day®	11 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
998	**6 y**	**25.25**	**M**	**ED**	Fracture left arm	Painstop Day®	20 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1002	**6 y**	**18.8**	**F**	**OP**	Elbow fracture	Painstop Day®	14 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1005	**2 y**	**14.55**	**M**	**OP**	Thermal burn right forearm	Painstop Day®	12 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1012	**1 y**	**10.2**	**M**	**ED**	Viral illness	Painstop Day®	8 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1015	**7 y**		**F**	**IP**	Hearing loss, left cholesteatoma	Painstop Day®	18.5 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1052	**8 y**	**23.7**	**F**	**ED**	URTI, cough	Painstop Day®	18 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1053	**8 y**	**32.15**	**F**	**IP**	Congenital adrenal hyperplasia; adenotonsillectomy	Painstop Day®	25 mL qid 5/7	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1054	**7 y**	**36.24**	**M**	**IP**	Knee deformity and pain	Painstop Day®	25 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1060	**8 m**	**6.14**	**M**	**IP**	Caudal dysplasia sequence with imperforate anus	Painstop Day®	4 mL qid	liquid	PO	yes	no	OL	Age	MIMS: Do not use in infants under 12 months of age.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1064	**3 y**	**15.15**	**M**	**IP**	Spinal fracture	Painstop Day®	12 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1068	**4 y**	**17.2**	**M**	**IP**	Upper lip laceration, admitted after ED	Painstop Day®	12 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1083	**11 y**	**38**	**M**	**IP**	Laceration to lower leg	Painstop Day®	30 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1095	**5 y**	**20.3**	**M**	**IP**	Left-sided cochlear implant, seasonal allergic rhinitis	Painstop Day®	16 mL tds prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1111	**1 y**	**11.9**	**M**	**IP**	Laceration right hand, dehisced	Painstop Day®	10 mL qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1121	**6 y**	**26.9**	**F**	**ED**	Fracture right distal radius and ulna	Painstop Day®	21 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1127	**4 y**	**30.1**	**M**	**ED**	Scalp laceration	Painstop Day®	15 mL once	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
1136	**1 y**	**11**	**F**	**ED**	Tonsillitis, dehydration, admitted after seen in ED	Painstop Day®	8 mL qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL.
486	**7 m**		**F**	**ED**	Unsettled and irritable during the day.	Painstop Night®	4ml	oral	PO	yes	no	OL	Age	MIMS: Not for children under 2 years of age.
692	**3 y**		**F**	**IP**	Repair of ostium premiun defect and left AV valve regurgitation, small pericordial effusion	Painstop Night®	9.5mL QID prn	oral	PO	yes	no	OL	Dosage	MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL. Dose administered higher than recommended by MIMS
819	**1 y**	**11.65**	**M**	**IP**	Eyebrow laceration (infected), finger infection	Painstop Night®	8 mL once	liquid	PO	yes	no	OL	Age	MIMS: Not for children under 2 years of age.
824	**4 y**	**15.5**	**M**	**IP**	Periorbital cellulitis, laceration to eye glued on Sunday, swelling started Monday	Painstop Night®	12 mL qid prn	liquid	PO	yes	no	OL	Dosage	MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL. Dose administered higher than recommended by MIMS
1100	**4 y**	**17.15**	**M**	**IP**	Supracondylar elbow fracture	Painstop Night®	14 mL qid prn	liquid	PO	yes	no	OL	Dosage	MIMS: Children 1-2 years (10-12kg) 5-6mL; 2-3 years (12-14kg) 6-7mL; 3-4 years (14-16kg) 7-9mL; 4-5 years (16-18kg) 9-10mL; 5-6 years (18-20kg) 10-11mL; 6-7 years (20-22kg) 11-12mL; 7-8 years (22-24kg) 12-13mL; 8-9 years (25-28kg) 13-15mL; 9-10 years (28-32kg) 15mL. Dose administered higher than recommended by MIMS

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
816	9 y		M	IP	Circumcision (phimosis), asthma	Panadeine Forte®	1 qid prn	tab	PO	yes	no	OL	Dosage	MIMS: Children: 7-12 years: 1/2 tab; max 3 tabs/ day
910	8 m		M	ED	Reflux, vomiting	pantoprazole	16 mg/day	granules	PO	yes	no	OL	Age	MIMS: To date there is insufficient experience with treatment in children under 5 years to justify a general recommendation.
994	2 d	2.04	M	IP	Necrotising enterocolitis, short bowel syndrome	pantoprazole	5 mg daily	IV	IV	yes	no	OL	Age	MIMS: To date there has been no experience with treatment in children
18	5 y	30	F	IP	Possible appendicitis (abdominal pain). Admitted for appendectomy	paracetamol	500mg qid	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
32	5 m	8.9	M	ED	Viral illness	paracetamol	150mg	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
100	8 y	27.82	F	IP	Left supracondylar fracture	paracetamol	540mg QID prn	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
132	5 y	18.2	F	IP	Adenotonsillectomy	paracetamol	550mg - one dose only	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
181	7 y	26.25	M	IP	Fractured radius and ulna following a fall at school. Obvious deformity observed	paracetamol	500mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
219	10 y	44	M	IP	Adenoidectomy without tonsillectomy and cauterisation of nasal turbinates.	paracetamol	1000mg - one dose	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
246	9 y	44.35	F	ED	Slipped femoral epiphysis (pain on ambulation and there was obvious deformity and swelling, patient was admitted for hip pinning)	paracetamol	660mg QID	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
257	1.5 y		F	ED	Cellulitis (MRSA); 12 hours of fever, vomit, rash to abdomen. Ringworm found around buttock	paracetamol	220mg q6h	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
332	3 y	16.05	M	OP	Injury. Right upper limb and thumb fractured	paracetamol	300mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
339	1 y	9.6	M	ED	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	paracetamol	250mg (one dose)	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
358	6 y	26.45	M	ED	Injury - closed fracture	paracetamol	500mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
409	7 y	32.45	M	IP	Phimosis (elective admission). Patient was commenced on IV ondansetron 3mg QID prn.	paracetamol	600mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
428	2 y	15.9	M	ED	Viral illness (Fever, watery eyes, runny nose and sores in the mouth)	paracetamol	270mg	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
431	6 y	21.48	F	ED	Ingested a 10cent coin and was admitted for endoscopy and removal of foreign body	paracetamol	400mg QID prn	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
446	10 y	41.3	F	ED	Appendectomy.	paracetamol	800mg QID prn	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
458	9 y	37.3	F	IP	Tonsillectomy	paracetamol	740mg q6h	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
516	2 y	9.6	M	OP	Replantation of left thumb	paracetamol	200mg QID	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
536	3 y	11.7	F	ED	Viral illness, nausea	paracetamol	220mg QID	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
556	4 y	22.92	F	ED	Tonsillitis	paracetamol	450mg	oral liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
572	11 y	47.2	M	IP	Excision of congenital melanocytic nevus on left posterior thigh	paracetamol	700mg QID	tab	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
577	11 y	35.8	M	IP	Irritable bowel syndrome, constipation, weight loss	paracetamol	600mg qid prn	tab	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
605	8 y	34.5	F	IP	Cellulitis to ear	paracetamol	690mg QID prn	tab	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
607	8 y	20.6	M	IP	Cerebral palsy, spasticity, is receiving BTX-A injection	paracetamol	400mg QID prn	tab	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
643	9 y	33.7	F	IP	Diabetes Mellitus type 1, hypoglycaemia	paracetamol	600mg QID prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
653	7 y	29.8	M	IP	Hemithyroidectomy	paracetamol	500mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
705	6 m		M	IP	Bronchiolitis	paracetamol	150mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
720	10 y	44.1	M	IP	Right testicular hydratid torsion	paracetamol	800mg QID prn	oral	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
740	1 y 8 m	10.35	M	IP	Insertion of grommets	paracetamol	200mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
749	2 y	12.55	M	ED	Split lower lip, croup	paracetamol	240 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
754	11 y	39.3	M	IP	Injury to big toe, stubbed, swelling not improving	paracetamol	80 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
814	6 m	9.35	M	IP	Removal of bilateral preauricular skin tags and anterior tongue cyst	paracetamol	180 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
833	8 y	22.8	M	IP	Mosaic down syndrome, left tibial osteotomy and fibular epiphyseodesis, constipation	paracetamol	40 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
892	8 y	26.2	M	IP	Constipation: ACE-procedure, appendectomy	paracetamol	500 mg q6h prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
904	6 y	22.95	M	IP	Burn to left foot, skin grafts	paracetamol	450 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
944	1 y	8.68	F	IP	Bronchiolitis, LRTI	paracetamol	150 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
960	11 y	51.65	M	IP	AML, sepsis after 4th cycle of chemo	paracetamol	1000 mg qid prn	tab	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
962	2 y	17.65	M	IP	Cystic swelling to neck, infective exacerbation	paracetamol	350 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
988	3 y	14.35	M	IP	Facial laceration, sutured	paracetamol	280 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
994	2 d	2.04	M	IP	Necrotising enterocolitis, short bowel syndrome	paracetamol	53 mg = 26 mg/kg	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Neonates < 10 days: 7.5mg/kg up to 4 times daily.
1029	3 y	17.2	M	IP	Foreign body in nose	paracetamol	300 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1057	2 y	14.1	M	IP	Dental trauma, extraction	paracetamol	280 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1060	8 m	6.14	M	IP	Caudal dysplasia sequence with imperforate anus	paracetamol	125 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1095	5 y	20.3	M	IP	Left-sided cochlear implant, seasonal allergic rhinitis	paracetamol	400 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1101	2 y	11.7	M	IP	Hydronephrosis, iron deficiency anaemia	paracetamol	200 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1110	5 m	5.11	F	IP	Bilateral hernias, right ovary and fallopial tube prolapse	paracetamol	100 mg qid prn	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1111	1 y	11.9	M	IP	Laceration right hand, dehisced	paracetamol	200 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1139	11 m	8.8	M	IP	Jejunal atresia, bowel obstruction, vomiting	paracetamol	150 mg qid prn	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
1186	3 m	6.97	F	IP	RVS bronchiolitis	paracetamol	125 mg qid	liquid	PO	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: 15mg/kg 4 hrly up to 4x/day.
733	5 y	14.65	M	IP	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	parachoc	20 ml bd	liquid	PO	yes	no	OL	Dosage	MIMS: Children 12 mnths-6 yrs: 10-15 mL daily
132	5 y	18.2	F	IP	Adenotonsillectomy	parecoxib	20mg	IV	IV	yes	no	OL	Age	MIMS: Has not been studied in patients under 18 years old.. Therefore its use is not recommended in these patients.
205	5 y	19.75	M	IP	Adenoidectomy and cautery of turbinates	parecoxib	40mg	IV	IV	yes	no	OL	Age	MIMS: Has not been studied in patients under 18 years old.. Therefore its use is not recommended in these patients.
643	9 y	33.7	F	IP	Diabetes Mellitus type 1, hypoglycaemia	pizotifen	0.5 mg nocte	tab	PO	yes	no	OL	Age	MIMS/TGA: Experience in children is still limited.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
339	**1 y**	**9.6**	**M**	**ED**	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	potassium chloride	5mmol daily	oral	PO	no	no	UL	Formulation	PMH formulation
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	potassium chloride	1 tab bd	tab	PO	yes	no	OL	Age	MIMS: safety and effectiveness have not been established for use in children under 12
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	potassium chloride	20 mmol	liquid	PO	no	no	UL	Formulation	PMH formulation
669	**8 y**		**M**	**IP**	Malaria, schistosomiasis, tinea capitis, raised ALT	praziquantel	450 mg q4h for 3 doses	tab	PO	yes	no	OL	Age	MIMS: Safety in children has not been established
812	**6 y**	**25**	**F**	**IP**	Epilepsy, seizure with cyanotic episode, admitted after seen in ED; deceased 9/5/2010 (apnoea following LRTI and seizure)	pregabalin	75 mg bd	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of pregabalin has not been established in patients below the age of 18 years
549	**1 y 8 m**	**17.4**	**M**	**IP**	Burns to face, chin, neck, chest, right arm (8% BSA), admitted for 18 days, skin graft	promethazine	5.5 mg qid prn	liquid	PO	yes	no	OL	Age	MIMS: promethazine should not be used in children under 2 years of age due to the potential for fatal respiratory depression.
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	promethazine	1.5 mg	liquid	PO	yes	no	OL	Age	MIMS: This product should not be used in children under 2 years of age due to the potential for fatal respiratory depression.
797	**5 y**	**18.65**	**M**	**IP**	Allergic reaction	promethazine	45 mg	IM	IM	yes	no	OL	Age	MIMS: This product should not be used in children under 2 years of age due to the potential for fatal respiratory depression.
63	**2 y**	**14.1**	**M**	**IP**	Bronchiectasis (confirmed on a CT scan). Recently moved to Australia from Tanzania. PMH includes 2 episodes of pneumonia and mannose binding lectin (MBL) deficiency.	propofol	100 mcg	injection	IV	yes	no	OL	Age	MIMS: According to the manufacturer, propofol injection is not recommended in children under 3 years of age.
88	**1 y**	**11.4**	**F**	**ED**	Injury. Left upper limb. (patient was admitted for exploration and repair)	propofol	20 mcg	injection	IV	yes	no	OL	Age	MIMS: According to the manufacturer, propofol injection is not recommended in children under 3 years of age.
104	**2 y**	**15**	**M**	**IP**	Dentinogenesis imperfecta (Patient admitted for dental restoration and extraction)	propofol	30 mcg	injection	IV	yes	no	OL	Age	MIMS: According to the manufacturer, propofol injection is not recommended in children under 3 years of age.
266	**3 m**		**M**	**IP**	Elective left inguinal hernia repair (symptoms included vomiting and loose motions)	propofol	20 mcg	injection	IV	yes	no	OL	Age	MIMS: According to the manufacturer, propofol injection is not recommended in children under 3 years of age.
341	**1 y**		**M**	**IP**	Lesion in liver	propofol	30 mg	injection	IV	yes	no	OL	Age	MIMS: According to the manufacturer, propofol injection is not recommended in children under 3 years of age.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
476	**4 m**		**M**	**IP**	Posterior encephalocele (Patient admitted for MRI of brain and spine under GA)	propofol	20 mg	injection	IV	yes	no	OL	Age	MIMS: According to the manufacturer of Propofol Sandoz, propofol injection is not recommended in children under 3 years of age.
880	**1 y**		**M**	**IP**	Severe croup, asthma; transferred from JHC	propofol	40 mg	IV	IV	yes	no	OL	Age	MIMS: There are no clinical trials to support the use of propofol for the sedation of children with croup or epiglottitis receiving intensive care. MIMS: According to the manufacturer of Propofol Sandoz, injection is not recommended in children under 3 years of age.
485	**1 y**		**M**	**OP**	Review of coarction repair and duct litigation.	propranolol	2mg tds	oral	PO	yes	no	UL	Formulation	Hospital formulation.
114	**14 y**	**55**	**M**	**IP**	Injury after playing football. Also suicidal ideation and worsening depression.	quetiapine	50mg	oral	PO	yes	no	OL	Age	MIMS: The safety and efficacy have not been established in patients under 18 years of age.
193	**14 y**	**42**	**F**	**IP**	Post-traumatic disorder. Showed depressive features and multi-sensory hallucinations.	quetiapine	50mg	oral	PO	yes	no	OL	Age	MIMS: The safety and efficacy have not been established in patients under 18 years of age.
464	**16 y**	**64**	**M**	**ED**	Hit by a car travelling at 50km/hr. Mild headaches, blurred vision and vomiting (possible splenic injury). Patient's PMH includes behavioural issues. Was observed to be suicidal.	quetiapine	25mg daily	oral	PO	yes	no	OL	Age	MIMS: The safety and efficacy have not been established in patients under 18 years of age.
1036	**12 y**	**60**	**M**	**ED**	Chemical intoxication (vodka, cologne)	quetiapine	25 mg	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy have not been established in patients under 18 years of age.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	ranitidine	50 mg bd	liquid	PO	yes	no	OL	Age	MIMS: Experience in children is limited and such use has not been fully evaluated in clinical studies. Ranitidine, has however, been used successfully in children aged 8 to 18 years in doses up to 150mg twice daily
797	**5 y**	**18.65**	**M**	**IP**	Allergic reaction	ranitidine	18 mg	IV	PO	yes	no	OL	Age	MIMS: Experience in children is limited and such use has not been fully evaluated in clinical studies. Ranitidine, has however, been used successfully in children aged 8 to 18 years in doses up to 150mg twice daily
887	**1 y**		**M**	**IP**	Viral induced wheeze	ranitidine	2 mL (30 mg)	liquid	PO	yes	no	OL	Age	MIMS: Experience in children is limited and such use has not been fully evaluated in clinical studies. Ranitidine, has however, been used successfully in children aged 8 to 18 years in doses up to 150mg twice daily

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
925	14 y	58.2	F	OP	Epilepsy, psychosis, vitamin D deficiency	risperidone	1 mg daily	tab	PO	yes	no	OL	Age	MIMS: Experience is lacking in children with schizophrenia less than 15 years
28	1 y		F	ED	Possible bronchiolitis	salbutamol	6 puffs via spacer	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
62	1 y		M	ED	Virus induced wheeze (difficulty breathing and patient passed out and was floppy)	salbutamol	6 puffs QID	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
97	2 y		M	IP	Asthma (worsening shortness of breath, cough)	salbutamol nebules	6 puffs inhaled every 1/2 - 2 hourly	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
97	2 y		M	IP	Asthma (worsening shortness of breath, cough)	salbutamol	6 puffs inhaled every 1/2 - 2 hourly	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
136	3 y		M	ED	Cough, wheezing; diagnosed with moderate-severe asthma.	salbutamol	4 puffs inhaled every 1 - 2 hours as needed	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
144	11 m		M	ED	Respiratory distress was seen yesterday morning and diagnosed with bronchiolitis. Overnight increased respiratory effort and wheeze	salbutamol	6 puffs every 20 min	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
160	6 y		M	ED	Worsening asthma and cough	salbutamol	6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
272	4 y	16.9	M	ED	Viral pneumonitis (patient was pale, tachypnoeic and moderate intercostal muscle recession. (CXR showed no consolidation but bilateral infiltrates)	salbutamol	6 puffs - 3 doses every 20 min in ED	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
278	7 y		M	IP	Croup (Symptoms included sore throat, fever and not being able to breathe)	salbutamol	6 puffs in ED	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
288	10 m		F	ED	Viral URTI (3 day history of cough, rhinorrhea and vomiting)	salbutamol	6 puffs - 1 dose in ED	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
335	7 y		F	ED	Worsening asthma secondary to LRTI (Wheezing at home and appear cyanosed)	salbutamol	12 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
397	7 m	7.76	F	IP	Bronchiolitis (2-3 days of rhinorrhea, cough and wheeze)	salbutamol	6 puffs 3-4 hrly	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
418	**1.5 y**		**M**	**ED**	Viral induced wheeze. (Patient unwell for 2 days and has runny nose, cough, difficulty breathing and no stridor at that time)	salbutamol	6 puffs every 20 minutes prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
432	**2 y**		**M**	**IP**	Viral induced wheeze and when in hospital patient was diagnosed with asthma. (Symptoms - cough, vomiting, patient became very distressed and was using accessory muscles)	salbutamol	6 puffs every 2-3 hours	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
449	**6 m**		**F**	**ED**	Viral URTI (Bronchiolitis, wheezing cough but has no respiratory distress)	salbutamol	6 puffs - 2 doses in one hour	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
482	**3 y**		**F**	**IP**	Unwell with cough, flu but the symptoms got worse and patient had CXR which showed bilateral changes.	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
512	**3 y**		**F**	**IP**	LRTI	salbutamol	6 puffs q0.5-2h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
521	**1 y**		**F**	**ED**	Respiratory distress, cough, fever, pneumonia	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
523	**1 y**		**M**	**IP**	Subcoronal hypospadias repair	salbutamol	2-6 puffs q4-6h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
535	**1 y**		**M**	**IP**	Viral pneumonitis	salbutamol	6 puffs q2h prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
541	**1 y**		**M**	**ED**	Respiratory distress, vomiting	salbutamol	2-6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
623	**1 y 6 m**		**F**	**ED**	Wheeze, cough, unsettled	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
656	**1 y 3 m**		**F**	**IP**	Bronchiolitis	salbutamol	6 puffs q0.5 - 4 h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
670	**17 y**		**M**	**OP**	Cystic fibrosis, chest crackles	salbutamol	6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
687	**3 y**		**F**	**IP**	Adenotonsillectomy	salbutamol	2-6 puffs prn with spacer	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
705	**6 m**		**M**	**IP**	Bronchiolitis	salbutamol	6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
718	**11 y**		**M**	**ED**	Persistent asthma	salbutamol	12 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
724	**8 y**		**M**	**IP**	Asthma exacerbation, viral	salbutamol	12 puffs every 90 minutes	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
734	4 y		M	IP	Viral wheeze	salbutamol	6 puffs q2-4h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
750	2 y		M	ED	Asthma exacerbation, viral	salbutamol	6 puffs thrice	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
816	9 y		M	IP	Circumcision (phimosis), asthma	salbutamol	4-6 puffs qid	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
839	13 y	32.8	M	ED	Asthma, infrequent exacerbations, epilepsy	salbutamol	2-6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
858	1 y 8 m		F	ED	Mild pneumonia	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
865	3 m	7.21	M	ED	Bronchiolitis (recurrent)	salbutamol	6 puffs q4-6h prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
880	1 y		M	IP	Severe croup, asthma; transferred from JHC	salbutamol nebules	6 puffs q0.5-2h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
887	1 y		M	IP	Viral induced wheeze	salbutamol	6 puffs q0.5-2h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
995	4 y		M	OP	Asthma	salbutamol	2-6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1004	2 y	13.76	M	ED	Cough, asthma, URTI, viral illness	salbutamol	6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1013	5 y		F	IP	Asthma exacerbation	salbutamol	6 puffs q0.5-1h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1026	1 y 3 m		M	ED	Asthma, viral wheeze	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1052	8 y	23.7	F	ED	URTI, cough	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1103	2 y		M	IP	Asthma exacerbation	salbutamol	6 puffs q0.5-4h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1130	5 y 5 m		F	IP	Asthma (new onset)	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1132	1 y 9 m		M	ED	Asthma exacerbation	salbutamol	6 puffs q1-3h via spacer	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1144	8 m	9.36	M	IP	Bronchiolitis, rhinovirus	salbutamol	2.5 mg q2-4h	nebules	Inhalation	yes	no	OL	Age	MIMS: no dosage given for children < 4 years
1144	8 m	9.36	M	IP	Bronchiolitis, rhinovirus	salbutamol	6 puffs q2-4h prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1145	9 m	9.34	M	IP	Bronchiolitis	salbutamol	27 mcg	IV	IV	yes	no	OL	Age	TGA: No dosage listed for children < 2 year
1145	9 m	9.34	M	IP	Bronchiolitis	salbutamol	6 puffs prn	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1146	11 m	10.8	M	ED	Tonsillitis, viral illness, wheeze	salbutamol	4 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1187	6 y		F	ED	Asthma, mild exacerbation	salbutamol	6 puffs	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1193	13 y		M	IP	Asthma, allergic rhinitis, exacerbation	salbutamol	12 puffs q0.5-4h	inhaler	Inhalation	yes	no	OL	Dosage	MIMS: children: 1-2 inhalations, may repeat every 4 hrs
1047	13 y		F	OP	Psoriasis	salicylic acid/cetylpyridinium chloride	nocte scalp and flexures 30/30 mg/g	cream	Topical	no	no	UL	Formulation	Hospital formulation.
193	14 y	42	F	IP	Post-traumatic disorder. Showed depressive features and multi-sensory hallucinations.	sertraline	50mg	tab	PO	yes	no	OL	Age	MIMS: Sertraline should not be used in children and adolescents below the age of 18 years for the treatment of major depressive disorder
936	17 y	55.55	F	OP	Major depressive disorder, chronic costochondritis	sertraline	125 mg mane	tab	PO	yes	no	OL	Age	MIMS: Sertraline should not be used in children and adolescents below the age of 18 years for the treatment of major depressive disorder
527	1 m	3.04	M	IP	Complex congenital cyanotic heart disease, pulmonary hypertension	sildenafil	1.5 mg qid	oral	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in paediatric pulmonary hypertension patients have not been established (Revatio). 2mg/mL solution prepared by hospital pharmacy.
527	1 m	3.04	M	IP	Complex congenital cyanotic heart disease, pulmonary hypertension	sildenafil	1 mg qid	oral	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in paediatric pulmonary hypertension patients have not been established (Revatio). 2mg/mL solution prepared by hospital pharmacy.
156	4 y	20.55	M	IP	Swollen face, was urinating blood, decreased urine today, unwell. Asthmatic, recent tonsillitis. BP 150/90. Principal diagnosis: post streptococcal glomerulonephritis, pre-renal impairment, secondary hypertension, proteinuria	sodium bicarbonate	10 mL bd	oral	PO	no	yes	UL	Formulation	MIMS: No commercial oral preparation available. PMH prepare a 8.4% oral solution (1 mmol/mL)
827	3 m		F	IP	CF, pancreas insufficiency	sodium chloride	7 % solution tds	nebules	Inhalation	no	no	UL	Formulation	Not registered in Australia
934	16 y		M	IP	CF, constipation (8 days no stool)	sodium chloride	7% solution daily	nebules	Inhalation	no	no	UL	Formulation	Not registered in Australia
946	9 m		M	OP	CF, pancreas insufficiency, bronchiolitis	sodium chloride	7% solution; 2.5 ml tds	nebules	Inhalation	no	no	UL	Formulation	Not registered in Australia
961	3 m		F	IP	CF, pancreas insufficient	sodium chloride	7% solution; 1 ml qid	nebules	Inhalation	no	no	UL	Formulation	Not registered in Australia
1088	9 y		F	OP	Enuresis, constipation	solifenacin	5 mg daily	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not yet been established. Therefore, Vesicare should not be used in children.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1089	**10 y**		**M**	**OP**	Nocturnal enuresis	solifenacin	5 mg daily	tab	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not yet been established. Therefore, Vesicare should not be used in children.
523	**1 y**		**M**	**IP**	Subcoronal hypospadias repair	SOOV IT®	5/50 mg/g	ointment	Topical	yes	no	OL	Age	CMI: not intended for use in children below 2 years of age
579	**8 y**		**F**	**OP**	Eczema	tacrolimus	0.3 mg/gl	lotion	Topical	no	no	UL	Formulation	tacrolimus lotion not registered in Australia
587	**6 y**	**20.7**	**F**	**ED**	Right-sided pneumonia with pleural effusion	teicoplanin	200 mg daily	IV	IV	yes	no	OL	Age	TGA: No children's dosage listed.
193	14 y	42	F	IP	Post-traumatic disorder. Showed depressive features and multi-sensory hallucinations.	temazepam	10mg	oral	PO	yes	no	OL	Age	According to MIMS, safety and effectiveness has not been established in children less than 16 years of age.
567	14 y	59.7	F	ED	Goitre, tremor, tachycardia, thyrotoxicosis	temazepam	10 mg daily 5/7	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy of temazepam have not been established in children less than 16 years of age
717	13 y	46.85	M	IP	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	temazepam	10 mg nocte prn	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy of temazepam have not been established in children less than 16 years of age
804	14 y		F	IP	Burkitt's lymphoma	temazepam	20 mg	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy of temazepam have not been established in children less than 16 years of age
923	15 y		F	IP	Spondylo-epiphyseal dysplasia tarda pseaudorheumatoid arthritis; scoliosis, spinal fusion	temazepam	10 mg	tab	PO	yes	no	OL	Age	MIMS: The safety and efficacy of temazepam have not been established in children less than 16 years of age
669	**8 y**		**M**	**IP**	Malaria, schistosomiasis, tinea capitis, raised ALT	terbinafine	125 mg daily	1/2 tab	PO	yes	no	OL	Age	MIMS: There is no experience with terbinafine in children and its use cannot be recommended
18	**5 y**	**30**	**F**	**IP**	Possible appendicitis (abdominal pain). Admitted for appendectomy	ticarcillin with clavulanic acid	1000mg	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
18	**5 y**	**30**	**F**	**IP**	Possible appendicitis (abdominal pain). Admitted for appendectomy	ticarcillin with clavulanic acid	1500mg bd	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
63	**2 y**	**14.1**	**M**	**IP**	Bronchiectasis (confirmed on a CT scan). Recently moved to Australia from Tanzania. PMH includes 2 episodes of pneumonia and mannose binding lectin (MBL) deficiency.	ticarcillin with clavulanic acid	1200mg tds	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
91	**7 y**	**26**	**M**	**IP**	Acute appendicitis with perforation, admitted for laparoscopic appendectomy.	ticarcillin with clavulanic acid	1300mg QID	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
302	**13 y**		**M**	**ED**	Laparoscopic appendectomy.	ticarcillin with clavulanic acid	1000mg	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
316	**12 y**	**34.25**	**M**	**ED**	Acute appendicitis (Patient admitted and underwent laparoscopic appendectomy)	ticarcillin with clavulanic acid	1500mg during anaesthesia	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
316	**12 y**	**34.25**	**M**	**ED**	Acute appendicitis (Patient admitted and underwent laparoscopic appendectomy)	ticarcillin with clavulanic acid	1500mg QID	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
339	**1 y**	**9.6**	**M**	**ED**	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	ticarcillin with clavulanic acid	1000mg (one dose in ED)	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
400	**8 y**	**34.85**	**F**	**IP**	Patient complained of severe abdominal pain and was admitted (in-patient) for overnight observation.	ticarcillin with clavulanic acid	1700mg QID	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14. In hospital, patient was commenced on Timentin 1700mg QID. Timentin was classified as unlicensed and the reason for it was the indication for which it was prescribed. Patient was discharged the following day because symptoms were not consistent with appendicitis and analgesia was sufficient.
414	**7 y**	**47.85**	**M**	**ED**	Appendicitis. Patient was admitted for laparoscopic appendectomy.	ticarcillin with clavulanic acid	2500mg q6h	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
446	**10 y**	**41.3**	**F**	**ED**	Appendectomy.	ticarcillin with clavulanic acid	2000mg QID	IV	IV	yes	no	OL	Age	MIMS: safety and efficacy of Timentin has not been established in children under the age of 14.
500	**11 y**	**47.2**	**M**	**ED**	Severe abdominal pain. Patient was diagnosed with acute appendicitis and underwent urgent appendectomy.	ticarcillin with clavulanic acid	2350mg QID	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety of Timentin has not been established in infants and children under the age of 14
516	**2 y**	**9.6**	**M**	**OP**	Replantation of left thumb	ticarcillin with clavulanic acid	450 mg qid	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14
703	**13 y**		**M**	**IP**	Laceration to perianal area, wound infection	ticarcillin with clavulanic acid	2850 mg qid	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14
742	**10 m**	**7.47**	**M**	**IP**	Metopic craniosynosthosis	ticarcillin with clavulanic acid	375 mg qid	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
786	**13 y**		**M**	**ED**	Appendicitis	ticarcillin with clavulanic acid	2.5 mg qid	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14
873	**2 y 6 m**	**16.05**	**M**	**IP**	Total colonic Hirschsprungs disease; closure of ileostomy	ticarcillin with clavulanic acid	750 mg qid	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14
1074	**11 y**	**34.5**	**M**	**IP**	Appendectomy	ticarcillin with clavulanic acid	2000mg QID	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14
1116	**3 m**	**4.84**	**F**	**IP**	Cleft lip repair	ticarcillin with clavulanic acid	250 mg	IV	IV	yes	no	OL	Age	MIMS: The efficacy and safety have not been established in infants and children under the age of 14
1185	**4 m**		**M**	**OP**	Glaucoma, left exotropia	timolol	2.5 mg/ml daily BE	eye drops	Eye drops	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established by adequate and well controlled studies.
339	**1 y**	**9.6**	**M**	**ED**	Osteomylitis and pneumonia (staph aureus). Other diagnoses includes pneumothorax, gardia and thrombocytosis.	tinidazole	200mg	oral	PO	yes	no	UL	Formulation	PMH formulation
532	**13 y**	**50.5**	**M**	**OP**	Cystic fibrosis, pancreas insufficiency and bronchiectasis	tobramycin	80 mg bd	nebules	Inhalation	yes	no	OL	ROA	MIMS: Tobramycin solution for injection may be given IM or IV. In this case, used for inhalation.
544	**8 m**		**M**	**OP**	CF	tobramycin	80 mg bd	nebules	Inhalation	yes	no	OL	ROA	MIMS: Tobramycin solution for injection may be given IM or IV. In this case, used for inhalation.
584	**3 y**	**14.25**	**F**	**IP**	Pre-B ALL	tobramycin	180 mg daily	IV	IV	yes	no	OL	Dosage	Greater than dose specified in MIMS. MIMS: Adult dose for serious infections is 3mg/kg/day in 3 doses given every 8 hours. Life threatening infections: 5mg/kg/day
641	**3 y**		**F**	**OP**	CF	tobramycin	80 mg bd	nebules	Inhalation	yes	no	OL	ROA	MIMS: Tobramycin solution for injection may be given IM or IV. In this case, used for inhalation.
717	**13 y**	**46.85**	**M**	**IP**	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	tobramycin	450mg daily	IV	IV	yes	no	OL	Dosage	Greater than dose specified in MIMS. MIMS: Adult dose for serious infections is 3mg/kg/day in 3 doses given every 8 hours. Life threatening infections: 5mg/kg/day
934	**16 y**		**M**	**IP**	CF, constipation (8 days no stool)	tobramycin	500 mg daily = 8.16 mg/kg/day	IV	IV	yes	no	OL	Dosage	Greater than dose specified in MIMS. MIMS: Adult dose for serious infections is 3mg/kg/day in 3 doses given every 8 hours. Life threatening infections: 5mg/kg/day
934	**16 y**		**M**	**IP**	CF, constipation (8 days no stool)	tobramycin	80 mg bd	nebules	Inhalation	no	no	OL	ROA	MIMS: Tobramycin solution for injection may be given IM or IV. In this case, used for inhalation.
867	**12 y**	**32.8**	**F**	**IP**	Lymphoproliferative disease, Castleman's disease	tocilizumab	600 mg 3 weekly	IV	IV	no	no	UL	Not registered	Not registered in Australia

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
1088	**9 y**		**F**	**OP**	Enuresis, constipation	tolterodine	2 mg bd	tab	PO	yes	no	OL	Age	MIMS: The safety and effectiveness of Detrusitol in paediatric patients have not been established
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	topotecan	0.52 mg; 0.75 mg/m2	IV	IV	yes	no	OL	Age	MIMS: The use of topotecan in children is not recommended as only limited data are available
948	**4 y**	**17.3**	**F**	**IP**	Abdominal neuroblastoma; deceased 1/5/2010	topotecan	0.52 mg; 0.75 mg/m2	IV	IV	yes	no	OL	Age	MIMS: The use of topotecan in children is not recommended as only limited data are available
1099	**4 y**		**M**	**OP**	Right exotropia, right high myopia, left emmetropia	tropicamide	1 drop BE; 10 mg/ml	eye drops	Eye drops	yes	no	OL	Age	MIMS: Tropicamide has been reported to be inadequate for cycloplegia in children. Avoid use in children.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	tropisetron	5 mg daily	IV	IV	yes	no	OL	Age	MIMS: Since experience with Navoban in children is still limited, its use cannot be recommended.
1047	**13 y**		**F**	**OP**	Psoriasis	Upton's Paste	ASA 60%, TCAA 10%, glycerol 20%; prn to warts	ointment	Topical	no	no	UL	Formulation	not a registered product; hospital formulation
283	**3 y**		**M**	**OP**	HSV ulceration of the cornea. Pain/sensitive to light - patient treated for blepharitis for many months.	valaciclovir	280mg tds for 2 months	oral	PO	yes	no	OL	Age	MIMS: Safety and effectiveness in children have not been established. Dose in children: No data available.
1137	**1 y 3 m**	**9.6**	**M**	**OP**	Review for liver transplanted	valganciclovir	2.7 ml daily	liquid	PO	yes	no	OL	Age	MIMS: Safety and efficacy have not been established in this patient population. The use of Valcyte in children is not recommended because the pharmacokinetic characteristics of Valcyte have not been established in this patient population.
498	**16 y**		**M**	**IP**	Hodgkin Lymphoma (diagnosed in 2006)	vancomycin	1000mg q6h	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults - 0.5g every 6 hours or 1 g every 12 hours.
717	**13 y**	**46.85**	**M**	**IP**	Lymphoproliferative disease, EBV induced, admitted 24.10.08. - 01.12.08. deceased	vancomycin	930mg tds	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Adults - 0.5g every 6 hours or 1 g every 12 hours.
733	**5 y**	**14.65**	**M**	**IP**	Relapsed stage IV neuroblastoma, CNS disease, seizure control; deceased 30.8.08	vancomycin	320mg tds	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children: 15mg/kg loading dose then 10mg/kg every 6 hours.
945	**10 m**	**8.6**	**M**	**ED**	Impetigo	vancomycin	130 mg qid over 2 hours	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children: 15mg/kg loading dose then 10mg/kg every 6 hours.

Case ID	Age	Weight (kg)	Sex	IP, OP or ED	Diagnosis	Drug(s)	Dosage	Form	Route	Reg	Lic	OL/ UL	Reason OL or UL	Explanation for classification
960	**11 y**	**51.65**	**M**	**IP**	AML, sepsis after 4th cycle of chemo	vancomycin	1000 mg tds = 58 mg/kg/day	IV	IV	yes	no	OL	Dosage	Greater dose than specified in MIMS. MIMS: Children: 15mg/kg loading dose then 10mg/kg every 6 hours.
807	**7 m**	**5.26**	**F**	**IP**	CP, seizures and spasms, lissencephaly	vigabatrin	500 mg daily	liquid	PO	yes	no	OL	Age	MIMS: no dosage given for children < 3 years
946	**9 m**		**M**	**OP**	CF, pancreas insufficiency, bronchiolitis	Vitabdeck®	1/2 capsule daily	caps	PO	yes	no	OL	Age	MIMS: Children 4-10 yrs: 1 cap daily; adults, children > 10 yrs: 2 caps daily. No dose for children < 4 years(Vitabdeck drops should be used in children < 4 year)
961	**3 m**		**F**	**IP**	CF, pancreas insufficient	Vitabdeck®	1 cap daily	caps	PO	yes	no	OL	Age	MIMS: Children 4-10 yrs: 1 cap daily; adults, children > 10 yrs: 2 caps daily. No dose for children < 4 years(Vitabdeck drops should be used in children < 4 year)