Public Assessment Report

Decentralised Procedure

Lidocaine 4% w/w Cream

(lidocaine)

Procedure No: UK/H/5617/001/DC

UK Licence No: PL 20685/0038

Ferndale Pharmaceuticals Ltd
LAY SUMMARY
Lidocaine 4% w/w Cream
(lidocaine)

This is a summary of the public assessment report (PAR) for Lidocaine 4% w/w Cream (PL 20685/0038; UK/H/5617/001/DC). It explains how Lidocaine 4% w/w Cream was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Lidocaine 4% w/w Cream.

For practical information about using Lidocaine 4% w/w Cream, patients should read the package leaflet or contact their doctor or pharmacist.

What is Lidocaine 4% w/w Cream and what is it used for?
Lidocaine 4% w/w Cream is a type of medicine called a local anaesthetic, used to numb an area of the body in adults and children aged one month and older. It may be used prior to taking a blood sample or prior to administering a medicine by injection.

It may also be used to numb the skin prior to administration of painful topical treatments on larger surface areas of intact skin for adults only.

How does Lidocaine 4% w/w Cream work?
Lidocaine 4% w/w Cream contains the active ingredient lidocaine which temporarily numbs the surface of the skin, providing pain relief when a needle is inserted into a vein (venipuncture or venous cannulation) for medical purposes, such as extracting blood for laboratory tests.

How is Lidocaine 4% w/w Cream used?
The cream is applied in a uniform thick layer to the skin before a medical procedure starts.

Lidocaine 4% w/w Cream should be applied exactly as described in the leaflet or as directed by a doctor or pharmacist. Patients should check with their doctor or pharmacist if they are not sure.

Lidocaine 4% w/w Cream is for external use only. The cream should not be applied to raw or blistered skin, where there is a skin rash or eczema, or where there are cuts, grazes or wounds. It should also not be applied in the ear, inside the nose, in the mouth, to the anus (back passage), or genital mucosa. Patients should avoid getting Lidocaine 4% w/w Cream in their eyes, as it may cause severe irritation. If it accidentally gets in the eye, the eye should immediately be rinsed well with lukewarm water or sodium chloride (salt) solution and protected until sensation returns.

Applying Lidocaine 4% w/w Cream to the skin may result in temporary blanching (taking on a whitish appearance) followed by temporary redness of the site of application. Application to larger areas or for longer times than recommended could cause serious adverse effects due to the absorption of lidocaine.

Lidocaine 4% w/w Cream blocks all sensations in the treated area. Patients should avoid scratching, rubbing and exposure to extreme hot and cold until the anaesthetic effect has worn off.

For Venous cannulation or venipuncture:
The recommended dose to provide pain relief when inserting a needle into a vein is 1 g of cream which is approximately equal to a 5 cm length of cream squeezed from a 5 g tube or 3.5 cm squeezed from a 30 g tube.

Adults, including the elderly, and children over 1 year of age:
1 g to 2.5 g of cream is recommended, to cover an area of skin 2.5 cm x 2.5 cm (1” x 1”) where the needle
will be inserted. The cream should not be left on the skin for longer than 5 hours.

**Infants over 3 months but below 1 year of age:**
No more than 1 g of cream should be applied. The cream should not be left on the skin for longer than 4 hours.

**Infants over 1 month but below 3 months of age:**
No more than 1 g of cream should be applied. The cream should not be left on the skin for longer than 1 hour.

Use of Lidocaine 4% w/w Cream is not recommended for this indication in infants under one month of age.

**For Painful topical treatments on larger surface areas of intact skin:**
The recommended dose to provide anaesthesia prior to administration of painful topical treatments on larger surface areas of intact skin is 1 g of cream which is approximately equal to a 5 cm length of cream squeezed from a 5 g tube or 3.5 cm squeezed from a 30 g tube.

**Adults and the elderly aged 18 years and over:**
Use 1.5g to 2g on each 10cm² area of skin, to cover a maximum total area of 300 cm² (200 cm² is approximately equal to a face, 300 cm² to an arm). The recommended dose should not be exceeded.

The cream should not be reapplied for at least 12 hours after it has been removed.

Use of Lidocaine 4% w/w Cream is not recommended for this indication in patients below 18 years of age.

The medicine can be obtained without a prescription.

For further information on how Lidocaine 4% w/w Cream is used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

**What benefits of Lidocaine 4% w/w Cream have been shown in studies?**
The company provided literature data and new clinical data to support this application.
In these studies Lidocaine 4% w/w Cream was more effective than placebo at providing surface anaesthesia of the skin in patients requiring venipuncture cannulation and various surface surgical procedures.

**What are the possible side effects from Lidocaine 4% w/w Cream?**
Like all medicines, Lidocaine 4% w/w Cream can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Lidocaine 4% w/w Cream, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

**Why is Lidocaine 4% w/w Cream approved?**
The MHRA decided that the benefits of Lidocaine 4% w/w Cream are greater than its risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Lidocaine 4% w/w Cream?**
A risk management plan has been developed to ensure that Lidocaine 4% w/w Cream is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Lidocaine 4% w/w Cream, including the appropriate
precautions to be followed by healthcare professionals and patients.

**Other information about Lidocaine 4% w/w Cream**

Germany, Italy, Portugal, Spain, the Republic of Ireland, Sweden and the UK agreed to grant a Marketing Authorisation for Lidocaine 4% w/w Cream (PL 20685/0038; UK/H/5617/001/DC) on 04 October 2015. A Marketing Authorisation was granted in the UK on 06 November 2015.

The full PAR for Lidocaine 4% w/w Cream follows this summary. For more information about treatment with Lidocaine 4% w/w Cream, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in January 2016.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Lidocaine 4% w/w Cream (PL 20685/0038; UK/H/5617/001/DC) is approvable. This product can be obtained from a pharmacy (P).

Lidocaine 4% w/w Cream is a local anaesthetic for topical use to produce surface anaesthesia of the skin prior to:
- venous cannulation or venipuncture in adults and in the paediatric population ≥ one month
- administration of painful topical treatments on larger surface areas of intact skin where use of a topical anaesthetic is appropriate in adults only

The application was submitted using the Decentralised Procedure (DCP) with the UK as the RMS and Germany, Italy, Portugal, Spain, the Republic of Ireland and Sweden as CMSs. The application was submitted under Article 8(3) of Directive 2001/83/EC as amended (mixed application) for a known active substance.

This proposed product is identical to the UK nationally authorised product, LMX4 Lidocaine 4% Cream (PL 20685/0034; Ferndale Pharmaceutical Ltd), with the same formulation and indications. The applicant stated that the UK authorised LMX4 Lidocaine 4% Cream is the same as the United States (USA) licenced LMX4 (which was formerly called ELA-Max). Data referring to the ELA-Max and LMX4 brand names have been provided to support this application for Lidocaine 4% w/w Cream.

Lidocaine 4% w/w Cream is a topical anaesthetic containing 4% lidocaine in a lipid base. When this product is applied to intact skin it provides dermal analgesia by a release of lidocaine from the cream into the epidermal and dermal layers of the skin, and by the accumulation of lidocaine in the vicinity of pain receptors and nerve endings. Lidocaine is an amide-type local anaesthetic agent which stabilises neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby affecting local anaesthetic action. The main action is a blockade of voltage-dependent sodium channels. The onset, depth and duration of dermal analgesia provided by lidocaine depend primarily on the duration of application. Lidocaine 4% w/w Cream may cause transient peripheral vasoconstriction followed by transient vasodilation at the application site.

In support of the application the Applicant has submitted bibliographic data as well as original clinical data.

A satisfactory environmental risk assessment has been provided from literature-sourced data.

The applicant provided an acceptable risk management plan for this product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 04 October 2015). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 20685/0038) for this product on 06 November 2015.
II QUALITY ASPECTS

II.1 Introduction

The drug product is a white to off-white yellowish local anaesthetic cream and contains 40 mg of lidocaine per gram, as active ingredient. The excipients present are benzyl alcohol, carbomers, cholesterol, hydrogenated soy lecithin, polysorbate 80, propylene glycol, trolamine (for pH adjustment), all-rac-α-tocopheryl acetate and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The only excipient used that contains material of animal or human origin is cholesterol. The applicant has confirmed that this excipient is derived from sheep wool, and is sourced from non-BSE/TSE countries of origin.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of hydrogenated soy lecithin which complies with an in-house specification.

The finished product is packaged in either an aluminium tube with an epoxyphenolic internal lacquer fitted with a polypropylene screw cap or in an aluminium tube with a polyamide-imide internal lacquer fitted with a high density polyethylene screw cap containing 5 g and 30 g.

The following packaging options are approved but not all of these packaging options may be marketed:

1) A carton containing one 5g tube.
2) A carton containing five 5g tubes.
3) A carton containing one 5g tube with two Tegaderm® occlusive dressings.
4) A carton containing five 5g tubes with ten Tegaderm® occlusive dressings.
5) A carton containing one 30g tube.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Lidocaine

Chemical name(s): 2’, 6’-acetoxylidide, 2-(diethylamino)-acetamide, 2-(diethyllamino)-N-(2,6-dimethylphenyl)-acetamide

Structure:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{H} \\
\text{CH}_3 \\
\text{O} \\
\text{N} \\
\text{CH}_3 \\
\text{CH}_3
\end{array}
\]

Molecular formula: C_{14}H_{22}N_{2}O

Molecular weight: 234.3 g/mol

Appearance: White to almost white crystalline powder.

Solubility: Lidocaine is practically insoluble in water, very soluble in alcohol and in methylene chloride, freely soluble in ether.

Lidocaine is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, lidocaine, is covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, topical cream containing 40 mg lidocaine per gram as active substance. The choice of excipients is justified and their functions explained.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf life of 3 years before opening with a storage condition “Do not freeze” is set. Once the tube is opened the product should be used within 6 months. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
This full application has been submitted in accordance with Article 8(3) (mixed application) of Directive 2001/83/EC, as amended for Lidocaine 4% w/w Cream.

The pharmacodynamic, pharmacokinetic and toxicological properties of lidocaine are well known. As lidocaine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
Lidocaine consists of an aromatic ring system linked by an amide bond to a tertiary amine group. This combination of a hydrophilic with a hydrophobic domain determines the pharmacodynamic properties of lidocaine.
Lidocaine blocks the initiation and propagation of action potentials by plugging the transmembrane pore of voltage-dependent Na\(^+\) channels, thus preventing the voltage-dependent increase in Na\(^+\) conductance. The potency of an anaesthetic increases roughly in proportion to its lipid/water partition coefficient, which therefore suggests it binds to an amphiphilic receptor site.

In a recent study a group investigated the effect of lidocaine hydrochloride on the thickness of the neuronal and model membrane, to further understand the anaesthetic mode of action of lidocaine. Lidocaine hydrochloride and the other local anaesthetics tested interact concurrently with neuronal cell membrane lipids while interacting with Na\(^+\) channels. This affects the fluidity of the neuronal membrane lipid bilayer, which could facilitate transfer of the anaesthetic across the membrane to the binding site.

The main unwanted effects of lidocaine involve the central nervous system (CNS) and the cardiovascular system, and they constitute the main source of hazard in the clinical use of lidocaine. Topical application blocks nerve conduction near the site of application, and upon topical application of lidocaine to intact skin, systemic absorption of lidocaine is negligible.

**Primary pharmacology**

The combination of a hydrophobic (aromatic ring) and hydrophilic (tertiary amine) moiety enables lidocaine to cross the cell membrane readily and to reach the intracellularly located receptor site of voltage-dependent sodium channels. The hydrophilic or charged form is responsible for the direct interaction with the ionic channel. Since lidocaine is a weak base, the local pH influences the ratio of the charge/uncharged form and, thus the effectivity of the entry of lidocaine into the channel.

The consequence of the blockade of Na\(^+\) entry by lidocaine through voltage-dependent sodium channels is the interruption of nerve conduction. Its action is restricted to the site of application and rapidly reverses upon diffusion from the site of action. In addition, lidocaine can also block K\(^+\) channels, at higher concentrations. More recently lidocaine has also been shown to affect a variety of additional ion channels and receptors such as K\(^+\) channels, Ca\(^{2+}\) channels, transient receptor potential vanilloid 1 (TRPV1) channels, NMDA receptors, AMPA receptors and GTP-binding protein coupling receptors. A study has shown that lidocaine has multiple inhibitory effects on muscle-type nicotinic acetylcholine receptors. These interactions, however, require drug concentrations higher than are expected with Lidocaine 4% w/w cream.

After topical application, lidocaine targets nerve endings in the dermis, prevents the propagation of nerve impulses such as pain and temperature sensations, thereby providing analgesia.

**Secondary Pharmacology**

Following systemic absorption, lidocaine may also affect cardiac sodium channels. As a consequence, the duration of the action potential is decreased and the functional refractory period is prolonged, thereby preventing ventricular arrhythmias. Lidocaine has anti-arrhythmic properties.

Young post-weaning Sprague-Dawley rats were used to investigate the dose-response and time-action parameters for lethality and cardiac antiarrhythmic protection. Severe cardiac arrhythmia was induced with a single intramuscular (i.m) application of theophylline (20 mg/kg). Lidocaine was intraperitoneally (i.p) administrated at a constant volume of 0.1 ml/100 g. The LD\(_{50}\) value determined 24 hour after drug application was 133 mg/kg. In order of onset, after 2 to 5 minutes, the lidocaine effect starts with a brief sedation, increase respiratory rate; tonic convulsions sequentially involving the head, neck, back and all 4 limbs; clonic convulsions primarily of the head, neck and forelimbs; greatly laboured respiration; death. Death occurred after 7 minutes and was due to respiratory arrest. The cardiac antiarrhythmic protection (CAP\(_{50}\) of 28 mg/kg) happened at one-half the LD\(_{50}\) and had a fast onset of action, after 1 to 5 minutes after drug administration. The faster onset and shorter duration of the anti-arrhythmic action of
lidocaine after one single administration in this animal model has been found comparable to that seen in man.

After intravenous (i.v) lidocaine administration for 60 minutes in pregnant sheep a transient fetal bradycardia was detected. The arterial concentrations of lidocaine were 2 - 5 µg/ml in the mother and 2 µg/ml in the fetus. This effect however seems to be related to a change in the fetal PaO₂ (arterial pressure of oxygen) and to a decrease in uterine blood flow more than to a direct effect in the heart.

Lidocaine may also affect the central nervous system (CNS), producing initially light-headedness, dizziness, sensory disturbances, restlessness, disorientation, and tremor, including convulsions. Central stimulation may be followed by depression and death due to respiratory failure. The potency of convulsions was examined in the rat and in sheep. In the sheep, injection of lidocaine into the jugular vein at a rate of 2 mg/kg/minute produced convulsions, hypotension, respiratory arrest, and finally circulatory collapse at plasma concentrations of about 40 pg/ml. Convulsions occurred at 5.9 mg/kg in pregnant ewes, at 5.8 mg/kg in not pregnant ewes, at 18.4 mg/kg in the newborns, and at 41.9 mg/kg in the fetuses. Lidocaine plasma concentrations associated with the onset of convulsions were not significantly different among the 4 groups (12.1; 11.7; 16.6; and 16.4 mg/ml). The data indicate that fetal and newborn sheep are not more sensitive to lidocaine than adults.

Lidocaine inhibited K⁺-evoked [³H] gamma aminobutyric acid (GABA) release from synaptosomes of rat brain in a concentration-dependent manner. The i.v. administration of 0.8 - 1.6 mg GABA protected rats against convulsions induced by lidocaine in a dose-dependent manner. The GABA system may be involved in the mechanism of local anaesthetic-induced convulsion. Lidocaine did not alter glutamic acid decarboxylase (GAD) or GABA transaminase (GABA-T) activity in vitro.

Since lidocaine effects are on membranes, the relative potency is related to their octanol-water partition coefficient, and the following cellular systems are inhibited by lidocaine: tubule polymerization, lymphocyte capping, various CA²⁺-regulated systems, sarcoplasmic reticulum CA²⁺-ATPase, mitochondrial electron transport, acetylcholine receptor, luciferase and membrane-bound acetylcholinesterase. This suggests that it binds to an amphiphilic receptor site. The effect of lidocaine hydrochloride on the thickness of the neuronal and model membrane was investigated to further understand the anaesthetic mode of action of lidocaine. It was shown that lidocaine hydrochloride and the other local anaesthetics tested interact concurrently with neuronal cell membrane lipids while interacting with Na⁺ channels. This affects the fluidity of the neuronal membrane lipid bilayer, which could facilitate transfer of the anaesthetic across the membrane to the binding site.

**Safety Pharmacology**

Topical application of lidocaine (4 or 5 %) in humans is associated with minimal systemic absorption and thus ensures a minimal risk for systemic toxicities. Mild skin reactions are the most common adverse effect, and so the safety of lidocaine depends on its absorption rate from the skin. Reduction in lidocaine absorption reduces the peak plasma level, and thus reduces the risk of lidocaine toxicity. By increasing lidocaine percutaneous absorption by application onto big body areas, with prolonged application periods or changes in drug delivery system increases systemic absorption and would then lead to the possibility of reaching toxic plasma levels.

The local anaesthetic effect is found in humans in concentrations of 0.5 to 2% when the drug is injected close to the nerve and 4% when applied topically to mucous membranes. Systemic therapeutic effects are typically observed above blood serum levels of 1 µg/ml, and this level is considered toxic following topical administration of lidocaine. The antiarrhythmic effect is dose-related over the plasma range of 1-5 µg/ml, but toxic CNS effects may begin at 5-6 µg/ml in non-medicated patients.

Systemic absorption of lidocaine following topical application is minimal across intact skin, and high
safe dosages have since been reported for the application of EMLA and LMX4 creams to intact skin up to over 1000 cm\(^2\) in area. It is recommended that topical lidocaine is not used on wounds or mucous membranes as this can result in rapid and extensive absorption, and could lead to toxic plasma levels and systemic adverse effects.

A study was performed to show the pharmacokinetics of EMLA when applied to a laceration versus intact skin application in Albino laboratory-bred strain mice (BALB-C). Blood levels were collected at 0, 10, 20, 30, 45, 60, 75 and 90 minutes post EMLA application. Maximum drug plasma concentration (C\(_{\text{max}}\)) and area under the drug plasma concentration–time curve (AUC) values of lidocaine were significantly increased by 448.6% and 161.5%, respectively, following application of EMLA to lacerated mouse skin in comparison with intact mouse skin.

Changes in skin physicochemical properties, hydration and structure of lipid and proteins will also affect lidocaine absorption.

**Pharmacodynamic Drug Interactions**

Verapamil, a calcium channel blocker with some local anaesthetic properties, increases the potential risk for local lidocaine toxicity in patients undergoing regional anaesthesia. Pre-treatment of mice with verapamil increased the mortality of mice by 74%. Benzodiazepines and barbiturates have been shown to elevate the convulsive threshold to lidocaine. Higher CD\(_{50}\) and LD\(_{50}\) values of lidocaine were found when female mice were pre-treated with i.m diazepam, lorazepam or midazolam. Lidocaine can reduce activity of human serum cholinesterase.

Propranolol, a β-receptor antagonist with local anaesthetic activity, reduces the hepatic clearance of lidocaine by the direct inhibition of hepatic microsomal enzymes. In some cases, the systemic clearance of lidocaine in humans has been reduced by as much as 40% as a result of concomitant propranolol administration. There have also been isolated cases of lidocaine toxicity reported as a result.

In addition, the concomitant administration of the histamine H\(_2\) receptor blocker cimetidine, which inhibits hepatic metabolism and displaces lidocaine from hepatic protein binding, and may increase plasma concentration and toxicity of lidocaine. Cimetidine may also reduce lidocaine clearance by reducing hepatic blood flow and lidocaine toxicity has occurred in some patients as a result. Thus, in patients treated with cimetidine lowering of the maintenance dose of lidocaine may be indicated.

Pre-treatment with the histamine H\(_2\) antagonist ranitidine resulted in only a slight (9%) reduction in lidocaine clearance, so use of H\(_2\) antagonists other than cimetidine may be preferable.

The pharmacology of lidocaine is well known and described in the literature and the applicant has provided an adequate review of the recent literature. The discussion related to safety pharmacology is limited however relating safety more to the level of topical absorption, rather than discussing specifics as is recommended in the relevant ICH guidance. It is accepted however that there is sufficient clinical experience with this compound and with topical administration and so further revision of the non-clinical part is not necessary.

**III.3 Pharmacokinetics**

Topical anaesthetics such as Lidocaine 4% w/w Cream/LMX4 are applied directly onto the skin to provide cutaneous analgesia by targeting free nerve endings in the dermis. Accordingly, the therapeutic efficacy of local skin anaesthetics does not rely on percutaneous drug absorption. However, significant systemic absorption of lidocaine could be associated with unwanted drug effects.

Specific pharmacokinetic studies with Lidocaine 4% w/w Cream in animals have not been performed, although there is considerable data available on the pharmacokinetic properties of lidocaine deriving
from its long-lasting and worldwide use as a local anaesthetic.

**Methods of Analysis**
These are briefly described in the literature. Plasma levels of lidocaine can be determined using high-performance liquid chromatography (HPLC) or gas-liquid chromatography, the latter having a detection limit of 0.3 µg/ml. A more sensitive HPLC assay with a limit of sensitivity of 0.05 nmol/ml for lidocaine in blood and 0.03 nmol/ml for its metabolites has also been developed.

**Absorption**
Lidocaine absorption following topical application is generally poor because lidocaine delivery through intact skin needs to cross the stratum corneum. Lidocaine is rapidly absorbed from mucous membranes or denuded skin such as wound surfaces and mucous membranes, and also after intracheal and bronchial administration.

The pharmacokinetics following topical administration to mouse skin has been reported, and is discussed earlier in this report. EMLA when applied to a laceration versus intact skin application in Albino laboratory-bred strain mice (BALB-C). Blood levels were collected at 0, 10, 20, 30, 45, 60, 75 and 90 minutes post EMLA application. Both Cmax and AUC were significantly increased following application of EMLA to lacerated mouse skin in comparison with intact mouse skin.

Since lidocaine is a weak base (pKa, 7.86), only a proportion of 10-20% of the drug is found uncharged at the pH of the skin (pH 6 - 7.2). This proportion of uncharged lidocaine is supposed to be distributed by penetration of the epidermis and dermis to reach the nerves. A more basic pH increases the fraction of uncharged lidocaine and thus cellular or dermal penetration, while a more acid pH increases the charged form and water solubility.

Percutaneous absorption of lidocaine (2%) from a gel ointment preparation was studied in male Wistar rats. Lidocaine (1.5 g of gel corresponding to 300 mg lidocaine) was applied on the abdominal site of the body and blood samples were collected via the jugular vein at different time points after administration. Systemic absorption of lidocaine was very poor since lidocaine was not detectable in serum. However, lidocaine applied with 1% limonene, a penetration enhancer, promoted lidocaine absorption and the following serum concentrations were found: 0.65, 0.85, 0.95 and 1.05 µg/ml after 1, 2, 4, and 8 hours, respectively.

In rats the pharmacokinetics of lidocaine to plasma and the brain were studied, as a measure of CNS toxicity. Lidocaine 0.5 mg/kg, bipuvicaine 0.1 mg/kg or levobupivacaine 0.1 mg/kg/min was continuously administered to rats for 2 hours. No symptoms of CNS toxicity were observed during the study. Plasma cerebral concentrations of total and unbound lidocaine were highest at the end of the infusion (174 mg/ml and 76 mg/ml respectively). Overall, the authors concluded that the results suggested that all of the anaesthetics studied are extensively distributed intracellularly or bind to proteins in the cerebral extracellular fluid.

Additional clinical studies have examined respective absorption properties of a variety of lidocaine topical formulations in healthy children and adults. These studies demonstrated that there is minimal systemic absorption of lidocaine from lidocaine-5% patches applied to healthy adults for 12-, 18- and 24 per day on 3 consecutive days. Mean maximum plasma concentrations have shown the lidocaine patch to possess a minimal risk for systemic toxicity as well as for drug – drug interactions. The lidocaine topical absorption varies also according to the localization and condition of the skin.

The incidence of adverse effects is very low even when lidocaine is applied topically over large surface areas of intact skin, and plasma concentrations were lower than considered toxic levels. The systemic toxicity of the main lidocaine metabolites has also been discussed, and exposure to these derivatives is
considered to be low following topical application owing to the low absorption of lidocaine from intact skin.

**Distribution**

Following absorption lidocaine is rapidly distributed within all body tissues, the apparent total volume of distribution being approximately 100 L. Distribution takes place according to a two-compartment model involving first the highly vascularised tissues and then the tissues poorly perfused. Lidocaine (1 mg/ml) was administered as a bolus dose, followed by a continuous infusion at 4 g/minute for the first hour, 2 mg/minute for the second hour, and 1 mg/minute for the next 46 hours. It was concluded that a two-compartment model best describes the plasma concentration of lidocaine infusion in patients undergoing heart surgery with cardiopulmonary bypass.

In rats plasma and brain pharmacokinetics of lidocaine was studied, as a measure of CNS toxicity. Lidocaine 0.5 mg/kg, bupivacaine 0.1 mg/kg or levobupivacaine 0.1 mg/kg/minute was continuously administered to rats for 2 hours. Plasma cerebral concentrations of total and unbound lidocaine were highest at the end of the infusion (174 mg/ml and 76 mg/ml respectively). The results of this study suggests that all of the anaesthetics studied are extensively distributed intracellularly or bind to proteins in the cerebral extracellular fluid.

Approximately 65% of lidocaine is bound to plasma protein. Lidocaine is markedly bound to α-acid glycoprotein, a protein that is increased after trauma, surgery, burns, and myocardial infarction, in chronic inflammatory disorders, and in cancer. Protein binding would be increased in these conditions but reduced in neonates.

Lidocaine crosses the blood-brain-barrier freely and has a fetal/maternal plasma ratio of 0.5 - 0.7. Several animal studies reported the rapidly transfer of lidocaine across the placenta into the fetus. Lidocaine is distributed by rapid uptake into highly perfused fetal organs, especially heart, brain and liver. Since lidocaine is a weak base, fetal acidosis causes an accumulation of lidocaine in the fetus, and this will elevate the possibility of toxic effects. High lidocaine blood levels could occur after lidocaine application at the time of parturition.

**Metabolism**

Lidocaine is largely metabolised in the liver by cytochrome P450 enzymes; only 3% is found unchanged in the urine. Neither drug nor metabolite has been detected in the bile and there is no entero-hepatic circulation.

Hydroxylation of the aromatic ring moiety of lidocaine to give 3-hydroxylidocaine has also been shown to be a secondary minor metabolic pathway.

Each of the de-ethylation metabolites MEGX and GX has antiarrhythmic activity, the monoethyl derivative (MEGX) and the glycineylidide (GX) being 33 – 83% and 10 – 42% as active as lidocaine, respectively. Severe hepatic disease or reduced portal blood flow to the liver (as in congestive cardiac failure) decrease the rate of lidocaine metabolism. Recently it has been shown that the MEGX and GX metabolites can also inhibit glycine uptake which may contribute to the antinociceptive effects of lidocaine that have been observed when lidocaine is applied systemically. Glycinexylidide is present in μg/ml concentrations in the plasma of patients treated with lidocaine infusions for 24 hour or more. The apparent volume of GX distribution is similar to that of lidocaine, and plasma levels of GX have been shown to persist longer than either lidocaine or MEGX owing to its elimination half-time of 10 hour being much longer than that of lidocaine.

Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Concomitant therapy with drugs that alter hepatic blood flow or induce drug-
metabolising microsomal enzymes can also affect the clearance of lidocaine.

**Excretion**

After the metabolism of lidocaine in the liver (cytochrome P450 3A4), metabolites and unchanged drug (approximately 10%) are excreted by the kidneys. More than the 98% of an absorbed dose of lidocaine can be recovered in the urine.

Lidocaine has an elimination half time \( t_{1/2} \) of 1.6 hour in adults. The elimination half-life in neonates (3.2 hours) is approximately twice that of adults. The half-life may be increased in cardiac and hepatic dysfunction. Renal impairment does not affect the clearance of lidocaine but accumulation of its active metabolites can occur and may lead to toxicity.

The excretion of lidocaine has been reported in breast milk, as is its primary metabolite, monoethylglycinexylidide. The potential transfer of the metabolite 2,6-xylidine from nursing mother to infant is of toxicological concern, as xylidine has been shown to be a nasal carcinogen in rats. Xylidine content of bovine and human milk following lidocaine administration was examined. Xylidine was found to be present at levels ranging from 14.5 to 66.0 parts per billion (ppb) in the bovine milk samples and at 1.6 ppb in the human milk sample. These results demonstrated that xylidine is transferrable to bovine and human milk, but at levels far below those which are associated with its carcinogenicity in experimental animals.

**Pharmacokinetic Drug Interactions**

The loss of dermal thickness averages about 20% in elderly. Cutaneous blood flow is reduced by about 60%. Subcutaneous fat diminishes with age, although the proportion of the body fat increases until age 70, and the fat distribution changes as well. These changes could modify the rate of absorption, and distribution of lidocaine and thereby its efficacy in elderly skin.

Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Concomitant therapy with drugs that alter hepatic blood flow or induced drug-metabolising microsomal enzymes can also affect the clearance of lidocaine and contribute to increase lidocaine toxicity.

Approximately 65% of lidocaine is bound to plasma protein, however in cancer and uraemia this value may be even higher in association with increased α,α-acid glycoprotein concentrations. The use of histamine H\(_2\) receptor blockers is discussed earlier, in patients treated with cimetidine a lowering of the maintenance dose of lidocaine may be indicated.

The effects related to use with propranolol, a beta-receptor antagonist with local anaesthetic activity, has been previously discussed in this report.

The non-clinical pharmacokinetics of topical lidocaine have been reported in published literature and these have been discussed in the non-clinical overview.

**III.4 Toxicology**

No toxicological programme has been performed with Lidocaine 4% w/w cream, non-clinical data is supplied from a number of published articles of which many were performed in the days when the principles and guidelines of good laboratory practice (GLP) had not yet been established. Additional toxicity data has been obtained from studies completed in humans with EMLA and lidocaine 4%w/w Cream/LMX4.

**Single dose toxicity**

Lethal doses have been established in mice and rats. These intraperitoneal studies were administering
extreme high-doses of lidocaine with LD50s of 85 to 133.1 mg/kg in mice and 133 mg/kg in rats. Lidocaine-induced toxic symptoms started within minutes, usually including brief sedation, increased respiratory rate; tonic convulsions sequentially involving the head, neck, back and all 4 limbs. In rats death was mainly due to respiratory arrest.

**Repeated-dose toxicity**
Studies are reported in rats and dogs via the intraperitoneal route. In addition, the applicant has included discussions from healthy adult human studies conducted with topical formulations of lidocaine, obtained from literature.

**Rats:**
Lidocaine (60 mg/kg) was injected i.p 5 times per week over a period of 8 weeks to male Sprague-Dawley rats. Lidocaine-treated animals exhibited a progressive development of abnormal eating behaviour and seizures. The animals became omniphagic, eating significantly more faeces, straw, and gauze than control animals. They also showed an increased susceptibility to convulsions with continued administration of high doses of this drug. In addition to the increased frequency of convulsions over time, there was a clear progression in the duration of seizure activity. Seizures occurring early in the course of lidocaine administration lasted 1 minute or less, but the duration increased progressively following subsequent injections until seizures persisted in intermittent episodes for as long as 45 minutes. During long-term application, seizures also commenced earlier after a lidocaine injection (1 to 2 minute versus 10-15 minute initially required). This might be due to increased plasma levels of convulsive lidocaine metabolites such as glycinexylidide, which reveals approximately 10 times higher elimination half-times as lidocaine.

**Dogs:**
Six dogs were infused i.v with lidocaine (8 mg/kg min) until seizures occurred. The average dose and arterial plasma concentration at seizure onset were 20.8 & 4.0 mg/kg and 47.2 & 5.4 μg/ml (mean + standard error of the mean (SEM), respectively. The mean onset and duration of seizures at this dose were 160 31 & 200 & 58 seconds, respectively. The margin of safety between convulsive and lethal dose was determined by administration of 2 times the convulsive dose 24 hour later. The average dose and plasma concentration of all animals at seizure onset were 41.7 + 8.0 mg/kg and 271 + 64.0 μg/ml, respectively. Two dogs died because of progressive hypotension, respiratory arrest, and finally cardiovascular collapse with an average peak plasma concentration of 469 μg/ml. No ventricular arrhythmias were observed. Twenty-four hours later 3 times the convulsive dose was administered to the survivors. Death occurred in 3 animals, again due to hypotension, respiratory arrest, and subsequent cardiovascular collapse. Although lidocaine was consistently devoid of arrhythmogenic activity, this study reveals a hazardous potential of this local anaesthetic upon repeated i.v application.

**Humans:**
In humans, a number of clinical studies have been reported using topical administration of lidocaine cream (for LMX4 and for EMLA), of a gel and of transdermal patches. These studies examined the absorption of lidocaine from each differing formulation, to determine a viable administration regime. Further discussion of this is provided in the clinical overview and is part of the overall clinical discussion.

**Genotoxicity**
The lidocaine metabolite 4-hydroxy-2,6-dimethylaniline has been reported to be mutagenic in *Salmonella typhimurium* strain TA100, whereas no evidence of mutagenicity of lidocaine or its N-hydroxyamidine and N-hydroxylamine metabolites was revealed in the Salmonella tester strain TA1538. In addition, using a combined technique with chemical-ionisation mass spectrometry and stable isotope labelling failed to demonstrate a potentially mutagenic effect of the N-hydroxyamides found in human urine after oral lidocaine administration or during i.v lidocaine infusion for the
treatment of ventricular arrhythmias. It was concluded that lidocaine is a drug with low attendant risk if used as recommended.

One study assessed the genotoxicity of lidocaine in the Drosophila wing-spot test. The wing-spot test detected simultaneously point and chromosomal mutations as well as recombination induced by the indirect and direct action of genotoxins. Different doses of lidocaine anaesthetic were administered orally for 48 hour to third stage larvae with negative controls.

No in vivo mutagenicity studies in accordance with ICH S2 Genotoxicity Studies have been reported.

The results indicate that lidocaine is not mutagenic.

Three literature articles are discussed, and although these studies are not in accordance with recent ICH Guidelines for genotoxicity testing, due to the widely used nature of the active drug substance the general findings of these studies are accepted.

Carcinogenicity
2,6-xylidine, a metabolite of lidocaine, has been shown to be carcinogenic in rats. This metabolite has been detected in human tissue. 2,6-Xylidine was detected in human liver slices obtained from 5 individuals upon incubation with either lidocaine (100 µM) or monoethylglycinexylidide (100 µM) over a period of 4 hours in concentrations of 9.8 µM ± 2.1 (mean ± SD) and 7.9 ± 2.1 µM, respectively. However, when applied topically on intact skin only a small portion of lidocaine is able to enter the circulation and so a significant formation of 2,6-xylidine is not expected. Literature searches do not provide any evidence for the formation of 2,6-xylidine in skin following topical application of lidocaine.

The in vitro and in vivo methaemoglobinaemic potential of xylidine isomers were investigated in the rat. The in vitro experiment showed each of the xylidine isomers induced significant methaemoglobinaemia formation in the presence of active hepatic fractions. However, the in vivo study revealed that only 3,5-xylidine induced significant methaemoglobinaemia in rats. It was concluded that the differences were due to additional enzymatic pathways mediated by the high Km enzymes operative at the high incubation temperatures used in vitro, and that 3,5-xylidine is likely to be the only active isomer in the Sprague-Dawley rat at low exposure levels.

In a study to determine the genotoxic potential of 2,6-xylidine and one of its key metabolites, dimethylphenyl N-hydroxylamine (DHMA), despite the use of various metabolic conditions none of these compounds exhibited mutagenic effects in these Ames tests.

One of the metabolites of lidocaine, 2,6-xylidine has been shown to be a rat carcinogen, although no clinical signal has been raised following a review of relevant literature. It is also noted that amounts of this metabolite may be limited given the extent of absorption through skin and it has not been identified as a potential mutagen in Ames tests. Given the route of administration, vast clinical experience and the limited exposure to this compound, the expert’s conclusions can be accepted.

Reproductive and developmental toxicity
Lidocaine has been shown not to be teratogenic when administrated at any stage of pregnancy. Epidural analgesia in pregnant women immediately prior to delivery with lidocaine 1.5% caused no adverse effect on baseline fetal heart rate, uterine activity, neonatal acid-base status and neuronal adaptive capacity.

The effects of lidocaine on fetal murine CNS development in pregnant mice has been investigated. Lidocaine was administered i.p at gestational day 9 under light ether anaesthesia. On day 13 of gestation, the animals were killed by cervical dislocation. The dilation of the fourth ventricle was the
most frequent anomaly observed with lidocaine, however doses up to 40 mg/kg did not reveal a major teratogenic effect.

The reproductive and teratogenic effects of lidocaine were studied in 155 Sprague-Dawley rats with subcutaneously implanted osmotic minipumps. Rats were exposed for 2 weeks to 3 different doses of lidocaine (100, 250 and 500 mg/kg per day). Only a reduction in mean fetal weight was observed upon of the highest dose (500 mg/kg), and was considered to be secondary to delayed fetal development. No significant adverse reproductive and teratogenic effects were found. These findings were further supported by other studies, however it is also suggested that prenatal exposure to lidocaine may result in behavioural changes of offspring.

In pregnant ewes, lidocaine was administered intravenously at a rate to maintain plasma levels between 2-4 µg/ml (corresponding to concentrations reached in regional anesthesia). There were no changes to maternal blood pressure, pulse rate, cardiac output, stroke volume, uterine blood flow or intra-amniotic pressure. Fetus maintained blood pressure and stable pulse rate.

An in vitro study was conducted to examine the teratogenic effects of lidocaine in rat embryos. Sprague-Dawley rats were explanted on gestational day 9 and were cultured in medium containing various concentrations of lidocaine. After 50 hours of culture they were evaluated for growth size and morphology, including neural tube closure. The results of the study indicated that lidocaine only causes teratogenic effects in vitro at concentrations much higher than clinically relevant.

Effects on reproduction of high doses of lidocaine have been reported in the literature. Lidocaine has been reported to be non-teratogenic following use in animals (mice, rats and ewes), and this was confirmed following reviews of clinical data in humans. Potential exposure to lidocaine via the topical route would also limit a potential risk.

Local Tolerance
Local toxicity of lidocaine was evaluated in the rabbit which were injected i.m with 1 ml lidocaine (1%). In this study, lidocaine caused only slight symptoms of necrosis but no haemorrhage.

The primary skin irritation or corrosion potential of Lidocaine 4%w/w cream was investigated using a single 24-hour patch application to the abraded and unabraded skin of 3 male and 3 female New Zealand white rabbits in accordance with the organisation for Economic Co-operation and Development (OECD) GLP guidelines. Only a very slight to slight signs of erythema or edema were transiently observed 24 hours after removal of the LMX4 (4% lidocaine) patches both at the abraded and unabraded sites. None of the control (vehicle) sites showed any signs of irritation. LMX4 demonstrated only a mild irritant potential even after prolonged application, lidocaine 4%w/w cream is tolerable beyond the proposed application times of 30 to 60 minutes and up to 5 hours.

Allergic reactions upon topical application with lidocaine are rare but some have been reported and are characterised by cutaneous lesions, urticaria, oedema or, in the most severe cases, anaphylactic shock. Further discussion of local tolerance issues are also provided following human topical dosing with LMX4. In children, more than 85% treated with LMX4 (2.5 g, 30-minute application, without occlusion) did not present skin reactions of any type. Other clinical studies with the LMX4 (4% lidocaine) formulation support a lack of severe adverse events following administration. Clinical data also suggests that a lidocaine 4%w/w cream has limited irritation potential.

Other Toxicity Studies
Immunotoxicity has been studied using both in vitro and in vivo studies in mice, and further discuss the cellular immune response in patients administered topical lidocaine to treat contact dermatitis. In vitro-exposure of mouse lymphocytes and macrophages for 24 hour resulted in inhibition of random
macrophage motility and in an interference with the production of macrophage migration inhibitory factor or its interaction with the cell surface. In addition mice treated with lidocaine i.p (25 mg/kg body weight 4 times a day for 7 days) immunocompetent cell function was impaired.

Studies in animals (guinea pigs) have shown that lidocaine has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to lidocaine in the external auditory canal only showed no abnormality.

Methemoglobinemia involves the oxidation of iron from ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state, which renders the haemoglobin unable to transport oxygen. This has been observed with the prilocaine component of EMLA cream and is considered the most important systemic adverse effect in EMLA. The contribution of lidocaine to this effect is questionable, and has been further described in the literature which suggests that methemoglobinemia occurs more frequently with prilocaine or benzocaine than with lidocaine.

**Excipients and Impurities**
The excipients are well-known, frequently used in pharmaceutical industry and described in the European pharmacopoeia, with the exception of hydrogenated soy lecithin which is controlled by an in-house specification.

An adequate review of potential genotoxicity and carcinogenicity have been provided. Lidocaine has been shown to be transferred via the placenta and in breast milk. Animal studies on reproductive and developmental toxicity did not demonstrate evidence for a significant teratogenic potential of lidocaine.

The residual solvents and excipients in the formulation are discussed and raise no toxicological concerns.

III.5 Ecotoxicity/environmental risk assessment (ERA)
The applicant has provided a detailed ERA from a literature data. This is acceptable. The proposed product is unlikely to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
This is a full decentralised application submitted in accordance with Article 8(3) (mixed application) of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of lidocaine are well known. The applicant has provided new clinical data as well as literature references to support the application. This is considered appropriate.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
**Absorption**
Lidocaine is poorly absorbed through intact skin. It is however absorbed through damaged skin, from mucous membranes and the gastro-intestinal tract, and rapid absorption is seen from injection sites, including muscle.
**Distribution**

Lidocaine is widely distributed through highly perfused tissues when administered intravenously with an approximate volume of distribution of 100L. Distribution takes place in accordance with a two compartment model, involving first highly vascular tissues such as spleen, lung and kidney, followed by more poorly perfused tissues. Approximately 65-70% of absorbed lidocaine binds to plasma proteins, including a 1 acid glycoprotein (AAG). The extent of the binding depends upon the concentration of the lidocaine and AAG. Lidocaine readily crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It has a fetal:maternal plasma ratio of approximately 0.5-0.7.

**Elimination**

Following an intravenous dose of lidocaine, plasma concentrations rapidly decline with an initial half-life of less than 30 minutes. The elimination half-life is 1 to 2 hours although this may be prolonged when infusions are given over 24 hours or hepatic blood flow is reduced. Approximately only 3% of lidocaine is excreted unchanged in the urine. Accumulation of the active metabolites of lidocaine can occur in patients with renal impairment. However, this does not appear to affect the clearance of lidocaine.

**Metabolism**

Lidocaine is predominantly metabolised by the liver and first pass metabolism is extensive; bioavailability is about 35% following oral administration. When administered, approximately 90% of the dose is dealkylated in the liver to form monoethyl glycinexylidide (MEGX) and glycine xylidide (GX). It is thought that both these metabolites may contribute to the therapeutic and toxic effects of lidocaine as their respective half-lives are longer than lidocaine and GX may accumulate during prolonged infusions. Lidocaine is not hydrolysed in plasma since it is an amide and the amide link is also sterically hindered. MEGX and GX can be metabolised further to monoethyl glycine and xylidide respectively. In man, xylidide is excreted in the urine as the further metabolite 4-hydroxy-2,6-dimethylaniline. Approximately only 3% of lidocaine is excreted unchanged in the urine. Accumulation of the active metabolites of lidocaine can occur in patients with renal impairment. However, this does not appear to affect the clearance of lidocaine.

**Pharmacokinetics of metabolites**

When administered, approximately 90% of the dose is dealkylated in the liver to form monoethyl glycinexylidide (MEGX) and glycine xylidide (GX). It is thought that both these metabolites may contribute to the therapeutic and toxic effects of lidocaine as their respective half-lives are longer than lidocaine and GX may accumulate during prolonged infusions.

The following studies were provided to support the indication venipuncture or cannulation:

**Study 1**

43 adult volunteers were randomized to either ELA-Max (ie Lidocaine 4%w/w Cream) or EMLA on the left arm and the other drug on the right arm 15-30 minutes prior to venipuncture. No occlusion was used for either product. Serum lidocaine levels were determined in the first ten subjects. All levels were <0.1 μg/ml, ie undetectable. This study provides useful and reassuring data on serum levels of lidocaine that can be expected when Lidocaine 4%w/w Cream is used clinically as proposed in adults.

**Study 2**

A double-randomized, blinded, crossover trial to assess the efficacy of Lidocaine 4%w/w Cream with EMLA was conducted. It involved 120 children aged 5-17 years. Patients were randomized into one of two regimens: the 30 minute regimen in which each patient received 30 minute applications of Lidocaine 4%w/w Cream (no occlusion) and EMLA (under occlusion) in random order; or the 60 minute regimen in which each patient received 60 minute applications of both products, both under occlusion, in random order. Ten Lidocaine 4%w/w Cream patients from the 60 minute regimen group
were randomly chosen to have serum lidocaine measurements. The mean age of these patients was 7.9 years. Nine patients had serum levels <0.2ug/mL and one had a level of 0.3ug/mL. The authors concluded that this indicated no clinically significant absorption of lidocaine from Lidocaine 4%w/w Cream when applied for 60 minutes with occlusion (twice the recommended duration).

**Study 3**
The objective of this open study was to examine the safety of Lidocaine 4%w/w Cream in 12 children (aged 2-5 years) by measuring the plasma levels of lidocaine, vital signs and adverse events following application to the skin. Three children who received EMLA were also evaluated. Lidocaine 4%w/w Cream was applied for 30 minutes without occlusion, EMLA was applied for 60 minutes under occlusion. Blood samples were taken immediately before application of the drug and at specified times throughout a four hour period after application. The results are tabulated below.

<table>
<thead>
<tr>
<th></th>
<th>( \text{C}_{\text{max}} ) (SD)</th>
<th>( \text{T}_{\text{max}} ) (SD)</th>
<th>Mean AUC 0-4 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMX4</td>
<td>6.68 (4.57)</td>
<td>3.33 (0.72)</td>
<td>15.57</td>
</tr>
<tr>
<td>EMLA</td>
<td>5.67</td>
<td>2.67</td>
<td>14.90</td>
</tr>
</tbody>
</table>

At the end of the 4 hour study period lidocaine concentrations were observed to be still rising, indicating the absorption effects were overriding the elimination effects. As a result it was not possible to estimate the AUC from time to infinity for the majority of subjects. Also the \( \text{C}_{\text{max}} \) for one third of the subjects was noted at the end of the study. It is possible therefore that the lidocaine concentrations had not reached maximum levels during the study. However, the levels reached after 4 hours were sufficiently far below potentially toxic levels to remove any potential concern about continued absorption after 4 hours.

**Study 4**
This open study involved a phospholipid formulation of lidocaine, chemically similar to Lidocaine 4%w/w Cream, but a 5% concentration was used as opposed to 4%. The study objective was to examine the absorption of 5% lidocaine in 15 subjects aged 12-18 years following a single 30 minute, 3g application under occlusion to a 25 cm² area of the forearm. Resulting blood levels of lidocaine were determined over a 24 hour period. \( \text{C}_{\text{max}} \) ranged from 1.7 to 3.6ng/mL. \( \text{T}_{\text{max}} \) ranged from 4.0 to 12 hours and averaged 7.6 hours. These levels are <1/1000 of the reported toxic plasma levels for lidocaine. It also provides evidence that there is no potentially harmful rise of lidocaine levels in the period between four and 24 hours after application.

The data presented above show that in amounts used for venipuncture and cannulation, systemic exposure is very low and well below levels that would give either a systemic effect and is very much below the toxic levels. The data is therefore reassuring that because of the low exposure the safety profile in this indication will be benign.

The Pharmacokinetics of lidocaine 4% liposomal cream were adequately characterised in adults and children. Due to a relative lack of trial pharmacokinetic (PK) data in the 2-5 year old age group, the Applicant was able to apply bibliographic and trial data, as well as supporting evidence and bridge data obtained for both younger and older children in order to infer the PK characteristics of this age group:

Overcoming the challenges, the increased risk of toxicity faced by the immature liver of the neonate was extensively discussed in PK review Article in the new born, Guideline on Paediatric Dosing on the Basis of Developmental Physiology and Pharmacokinetic Considerations and in a discussion of Impact of developmental pharmacology on paediatric study design. Since no toxicity in neonates, children or adults was demonstrated by the Applicant’s trial data (the pivotal study on 12 x 2-5 year olds, along with the supporting data from 26 neonates, 120 x 5-17 year olds, 15 x 12-18 year olds and 67 x adults), it was
accepted that toxicity was a very low possibility in the intervening 2-5 year old age range, whose hepatic function is more mature than the neonate’s.

**Pharmacokinetics in paediatrics (aged 1 month and older)**

Three 4% liposomal lidocaine pharmacokinetic studies (Studies 2, 3 and 5; total 462 patients) and 3 EMLA studies (studies 7, 8 and 9; total 60 patients) are presented specifically for the <6 year old age group. These include 2 studies specifically for the minimum 1 month+ cannulation age group – study 5 (4% liposomal lidocaine, 330 new-borns; 60 donated blood) and study 8 (EMLA, 38 neonates).

**Table 1**

Summaries of Pharmacokinetic Studies of Lidocaine 4% w/w Cream and similar lidocaine formulations – Venous Cannulation Procedures

<table>
<thead>
<tr>
<th>Reference or study number</th>
<th>Dosage Regimen</th>
<th>Patient Population</th>
<th>Number of Subjects (Gender)</th>
<th>Age Range (Mean)</th>
<th>Major Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patients randomized to ELA-Max or EMLA on one arm and remaining drug to the other arm for 15 mins. No occlusion for either drug. Pain rated on VAS. Serum lidocaine levels measured in 19 patients.</td>
<td>Healthy adult platelet donors.</td>
<td>10 Gender not specified</td>
<td>Not specified</td>
<td>Serum levels all below limit of detection (&lt;100ng/ml).</td>
</tr>
<tr>
<td>2</td>
<td>LMIX4 applied for 60 minutes under occlusion</td>
<td>Children undergoing venepuncture</td>
<td>120</td>
<td>5y – 17y (7.9)</td>
<td>Nine subjects had a Cmax of 200 ng/ml. One subject had a Cmax of 300 ng/ml. Conclusion: no clinically significant absorption of lidocaine after 60 mins occlusion.</td>
</tr>
<tr>
<td>3</td>
<td>12 children had a single 30 min application of 3g of ELA-Max to a 2x2 inch area of the arm. 3 children had a single 60 min application of EMLA.</td>
<td>Healthy volunteer children</td>
<td>15 (7M/8F)</td>
<td>2y – 5y (4.21)</td>
<td>Cmax and Tmax for LMIX4 = 6.56 (SD=4.57) and 3.33 (SD=0.72). Conclusion: no clinically significant absorption of lidocaine after 60 mins occlusion.</td>
</tr>
<tr>
<td>4</td>
<td>1 single 30 min application of 3g 5% liposomal lidocaine cream to 25cm² area of the forearm. Blood levels determined over a 24 hour period to confirm Tmax and Cmax not observed in 2001 study.</td>
<td>Healthy volunteer children</td>
<td>15 (12M/3F)</td>
<td>12-18 y (14.60)</td>
<td>Cmax ranged from 1.7 – 3.6 ng/ml (mean 2.5ng/ml) Tmax ranged from 4.0 – 12 hours (av 7.6 hours). Conclusion: All plasma levels 1/1000th of reported toxic levels for lidocaine even at actual Tmax.</td>
</tr>
<tr>
<td>5</td>
<td>Double-blind randomised, controlled, double-dummy trial</td>
<td>Children undergoing</td>
<td>330 Newborns (mean)</td>
<td>Mean plasma lidocaine level 44.6ng/ml (n=26), range 2.6ng – 217ng/ml.</td>
<td></td>
</tr>
<tr>
<td>Reference or study number</td>
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<tr>
<td>6</td>
<td>Single and multiple dose pharmaco-kinetic study with two active subjects, 24 27-64 years of age.</td>
<td>Healthy male or female subject</td>
<td>24</td>
<td>27-64 years of age.</td>
<td>Day 1 arithmetic mean lidocaine Cmax 6.0138±4.63μg/ml Repeat dose lidocaine Cmax is less than 3 x Day 1 Cmax. Day 1 geometric mean Cmax ratio LMX4:ELMA 145.24% instead of 160% as predicted by design lidocaine content (4.2.5) Lidocaine safety margin is more than 5-fold when compared with the minimum therapeutic range (1μg/ml). Safety margin increases to more than 25, when comparing to the upper limit of the therapeutic range (5000 ng/ml), and to even more if referring to the quoted toxic concentrations (from 6000 ng/ml) The measured 2,6-DMA concentrations (maximum 4.25 ng/ml) have a safety margin to the concentrations thought to be associated to carcinogenesis in rats of more than 10.</td>
</tr>
<tr>
<td>7</td>
<td>2g EMLA / 16cm², various skin sites with occlusion for 4h</td>
<td>Infants</td>
<td>22 (17M, 5F)</td>
<td>3-6m &amp; 6-12m</td>
<td>3-6m Lidocaine Cmax 127ng/ml 6-12m Lidocaine Cmax 155ng/ml All measured blood lidocaine levels were below 200ng/ml and this is well below systemic therapeutic levels and systemic toxic levels.</td>
</tr>
<tr>
<td>8</td>
<td>Double-blind randomised controlled study mixing EMLA for circumcision. 1g EMLA applied to penis with occlusion.</td>
<td>Healthy male newborns</td>
<td>38</td>
<td>Newborn, (1-3 days)</td>
<td>Only 23 subjects blood levels were above the limit of detection (20ng/ml). Highest lidocaine blood level 135ng/ml.</td>
</tr>
</tbody>
</table>

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<th>Reference or study number</th>
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</thead>
<tbody>
<tr>
<td>9</td>
<td>0.5g EMLA to the arm for 60 minutes.</td>
<td>Pre-term infants</td>
<td>Pre-term infants</td>
<td>Pre-term infants</td>
<td>No signs of clinical toxicity.</td>
</tr>
<tr>
<td>10</td>
<td>Lidocaine aerosol 500mg (100 mg/ml) single wound treatment</td>
<td>Hysterectomised patients</td>
<td>30</td>
<td>Unk</td>
<td>A single dose of lidocaine aerosol topically applied in the surgical wound improved analgesia during the first postoperative day with minimal risk of side effects.</td>
</tr>
<tr>
<td>11</td>
<td>2g EMLA, 4 skin areas totaling 10cm², for 4h before anaesthesia for minor surgical procedure</td>
<td>Infants less than 3 months</td>
<td>UnK</td>
<td>Unk</td>
<td>Mean Hb concentrations in the infants younger than 3 months were small. The enzyme capacity may be overloaded if administered at the same time as other MetHb-inducing agents. Concluded EMLA use should be restricted in this age group.</td>
</tr>
<tr>
<td>12</td>
<td>1 – 1.25 g topical anesthetic (lidocaine – strength unknown)</td>
<td>Very low birth weight infants</td>
<td>13</td>
<td>Unk</td>
<td>The topical lidocaine and prilocaine cream application attenuated the liability of vital signs during line insertion in very low birth weight infants, with no evidence of toxicity.</td>
</tr>
<tr>
<td>13</td>
<td>400mg or 800mg lignocaine (lidocaine) endorectally or as gel with/without spinal block.</td>
<td>Adults</td>
<td>35M</td>
<td>Mean 65y – 70y</td>
<td>Mean peak serum lidocaine concentration 0.06, 0.15 and 0.36μg/ml for the three treatment groups. Lidocaine administered endorectally gives very low lidocaine blood concentrations that are substantially below the systemic toxic level of 5μg/ml.</td>
</tr>
<tr>
<td>14</td>
<td>2% jelly (mean 21.4g) instilled into genitourinary tract prior to cystoscopy.</td>
<td>Adults</td>
<td>30 (15M, 15F)</td>
<td>21y – 81y (59.5y)</td>
<td>Blood samples monitored up to 190 minutes post- application showed maximum serum lidocaine concentrations of 0.2μg/ml well below the level of systemic lidocaine toxicity.</td>
</tr>
<tr>
<td>15</td>
<td>Transurethral administration of 400mg lidocaine gel prior to transurethral prostatectomy. 11 patients had additional lidocaine administered</td>
<td>Adults</td>
<td>30</td>
<td>57y – 78y (64.5y &amp; 68.2y for the 2 groups)</td>
<td>Mean peak plasma lidocaine concentrations of the two groups = 142±4mg/ml (additional lidocaine group) &amp; 72±2mg/ml. Lidocaine applied transurethrally results in safe systemic lidocaine levels.</td>
</tr>
</tbody>
</table>
### Table 2
Summaries of Pharmacokinetic Studies of Lidocaine 4% w/w Cream and similar lidocaine formulations – Large Surface Area Indication

<table>
<thead>
<tr>
<th>Reference or study number</th>
<th>Dosage Regimen</th>
<th>Patient Population</th>
<th>Number of Subjects (Gender)</th>
<th>Age Range (Mean)</th>
<th>Major Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Lidocaine applied 200mg intravenously (200mg), orally (300mg), or rectally (300mg) in a balanced crossover study.</td>
<td>Adults</td>
<td>9M</td>
<td>23y-26y</td>
<td>Mean rectal systemic lidocaine availability was higher than oral bioavailability in whole blood and plasma. Oral and intravenous lidocaine elimination t1/2 values were similar. Rectal t1/2 was slightly longer. Results suggest it is possible to partly avoid ‘first pass’ lidocaine metabolism by administration rectally rather than orally or intravenously.</td>
</tr>
<tr>
<td>17</td>
<td>Lidocaine 10% aerosol spray or 2% lidocaine gel applied to anterior nares and oropharynx prior to bronchoscopy. Mean total lidocaine dose 623mg ± 41.1mg.</td>
<td>Adults</td>
<td>41</td>
<td>Not specified</td>
<td>Lidocaine gel produced lower plasma lidocaine levels than lidocaine aerosol.</td>
</tr>
<tr>
<td>18</td>
<td>Xylocaine (lidocaine) 5% ointment or Xylocaine HCl (lidocaine) 2% jelly applied to endotracheal tubes prior to endoscopy.</td>
<td>Hospitalised adults requiring surgery</td>
<td>34 (29F, 14M)</td>
<td>18y – 60y</td>
<td>Mean study lidocaine dose = 63mg. Lidocaine blood levels peaked at 15minutes post-application and all were below 1ug/ml. Mean peak levels = 5ug/ml &amp; 8ug/ml (ointment &amp; jelly respectively).</td>
</tr>
<tr>
<td>19</td>
<td>2% lidocaine gel or solution applied to the throat for 20mins or 5mins respectively prior to gastroscopy.</td>
<td>Adults</td>
<td>20 (15M, 5F)</td>
<td>Mean 42.5y (solution group) 43.6y (gel group)</td>
<td>In the gel group serum lidocaine concentrations were observed approx. 15 mins after application, all &lt;0.5ug/ml. Blood lidocaine levels for the solution group rose to 0.5ug/ml 15 mins after completion of the anaesthesia. MEGX concentrations were also raised and correlated with serum lidocaine values.</td>
</tr>
<tr>
<td>20</td>
<td>EMLA applied to normal facial skin and normal/diseased arm skin. Doses: Face = 10g/100cm² with occlusion for 1 hour. Arm = 4-6g/25cm² for 1 hour.</td>
<td>Healthy volunteers, patients with plaque-type lesions, patients with atopic or contact dermatitis</td>
<td>13, 8, 3F</td>
<td>20y – 60y (20y – 60y)</td>
<td>Maximum plasma lidocaine values reached 2-2.5h after application to the face, or 5h after application to the arm. Levels found in patients with atopic dermatitis were 100x greater than normal skin &amp; absorption was faster with quicker onset to anaesthesia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference or study number</th>
<th>Dosage Regimen</th>
<th>Patient Population</th>
<th>Number of Subjects (Gender)</th>
<th>Age Range (Mean)</th>
<th>Major Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>30% lidocaine in acid mantel cream or acid mantel cream alone (control) applied to healthy male newborns prior to circumcision.</td>
<td>Neonates</td>
<td>30M (15M &amp; 15M)</td>
<td>Gestation age 37-42 weeks</td>
<td>Serum lidocaine content assayed in 14 patients receiving lidocaine cream – mean conc 0.27ug/ml. Topical application of 30% lidocaine cream is safe and efficacious for use in newborn circumcision procedures.</td>
</tr>
<tr>
<td>22</td>
<td>LMX4 applied to face and neck (2.5g or 5g/100cm² up to 600cm²), 30 or 60 minutes with/without occlusion. Subjects split into 4 groups.</td>
<td>Healthy adults</td>
<td>24</td>
<td>22y – 46y (29.3y)</td>
<td>Mean serum lidocaine levels were all well below systemic therapeutic level (1ug/ml). Occluded groups showed increased lidocaine absorption. Increasing exposure time from 30 to 60 minutes increased lidocaine absorption. Doubling the lidocaine dose (5g compared with 2.5g) doubled the serum MEGX concentration and increased lidocaine concentration by 50%.</td>
</tr>
<tr>
<td>23</td>
<td>30g/600cm² face &amp; neck LMX4 or EMLA 60 minutes occluded</td>
<td>Healthy adults</td>
<td>25</td>
<td>Adults</td>
<td>Lidocaine Cmax results. EMLA = 0.77ug/ml (average 0.436ug/ml) LMX4 = 0.335ug/ml Relative bioavailability (ratio AUC) EMLA/LMX4 = 2.11, opposite to that expected based solely on relative lidocaine content (5:6:4).</td>
</tr>
<tr>
<td>24</td>
<td>30g or 60g LMX4 applied with occlusion at 10g/100cm² to 300bs² (face) or 600cm² of the abdomen or thigh. Lidocaine and MEGX metabolite levels assessed.</td>
<td>Healthy adults</td>
<td>8 (Gender not specified)</td>
<td>21y – 75y</td>
<td>All lidocaine serum levels below limit of detection (0.5ng/mL).</td>
</tr>
<tr>
<td>25</td>
<td>26 Healthy subjects received a single treatment of 5g EMLA (reference) and three treatments of 5g LMX4 / 50cm² (test) over 1 or 3 consecutive days (first reference treatments separated by 7 days and not actively removed in between).</td>
<td>Healthy adults</td>
<td>24 (5 F, 19 M)</td>
<td>27y – 54y</td>
<td>Mean LMX4 day 1 Lidocaine Cmax = 15.6ng/mL; Day 3 mean Cmax = 31.1ng/mL. Highest recorded lidocaine Cmax = 172ng/mL. Comparative bioavailability (mean Lidocaine Cmax) EMLA/LMX4 = 145:42. Lidocaine t1/2 after LMX4 application = 23.6h. Serum lidocaine levels show lidocaine accumulation from repeat 24h doses, but Day 3 Cmax is less than 3 x Day 1 Cmax. Supports safety at a minimum of 12 h reapplication time for LIDIAN 4% w/w Cream.</td>
</tr>
</tbody>
</table>
IV.3 Pharmacodynamics

The applicant has provided three literature references which discussed the systemic and topical lidocaine pharmacodynamics.

Lidocaine is an amide local anaesthetic, so-named due to the amide link between the aromatic and intermediate chain moieties, which makes it resistant to plasma hydrolysis and more stable systemically than ester-derived local anaesthetics.

The local anaesthetic action of IV lidocaine is observed at 0.5% – 2.0% concentrations, much lower than the 4.0% concentration observed with topical use on mucous membranes. Systemic effects are typically observed at lidocaine blood levels greater than 1μg/mL, anti-arrhythmic blood levels are approximately 1.5 – 5.0μg/mL, and systemic toxicity is reported to be in the region of 5μg/mL.

Analgesic effect: Membrane stabilisation of nerve fibres to propagation of an action potential (AP) via blockade of intracellular membrane voltage-gated sodium (Na+) ion channels following a suprathreshold depolarisation (neural impulse). As sodium ion permeability is interrupted, progressive reduction in electrical excitability increases the activation threshold for AP propagation. The rate of rise of the action potential declines and neural impulse conduction slows. Accordingly, action-potential propagation is diminished and nerve conduction fails. Potassium (K+) ion flux is also affected at higher concentrations, according to animal studies.
Absorption of local anaesthetics requires a lipid state conferred by the aromatic portion which allows diffusion across the lipoprotein cell membrane. This lipid/water partition co-efficient determines potency. Uncharged, base form local anaesthetic drug is inversely proportional to the pKa of that agent. At pH 7.4 lidocaine has a pKa of 7.9, or ~35% unionised base. This is closer to the pH 5.5 of skin and accounts for the relatively fast onset of action compared with other anaesthetic agents with higher pKa values, such as bupivicane pKa 8.4. Smaller nerve fibres, such as c-fibre pain afferents, are blocked preferentially because the critical length over which the impulse can propagate is shorter. Larger motor fibres are much less susceptible.

Conversion to an ionised cationic state intracellularly must occur for analgesic effect. Both the aromatic and amine portions determine protein binding, which in turn determines duration of effect.

Absorption through skin is dependent on pKa, density of sweat glands, binding affinity and vehicle effects. Local anaesthetics have been shown to interact with neuronal cell membrane lipids and sodium channels concurrently, affecting neuronal membrane lipid bilayer fluidity, postulated to facilitate transfer of the anaesthetic across the membrane to the binding site.

Since neurohumoral transmission facilitates vital organ function, systemic toxicity is to be avoided:

Heart: reduces automaticity via a decrease in the rate of diastolic (phase 4) depolarisation, with little or no effect on the His-Purkinje system conduction. The duration of the action potential is decreased due again to the blockage of Na+ channels and the functional refractory period is prolonged at moderate doses. Therapeutically, lidocaine prevents ventricular arrhythmias and elevates the threshold for ventricular fibrillation as class 1B anti-arythmic.

Central Nervous System (CNS): systemically lidocaine may cause stimulation of the CNS - restlessness and tremor, frank convulsions, followed by depression and death due to failure of cardiorespiratory cerebellar function.

Intravenous (IV) administration without adrenaline is 1-2 mg/kg, the maximum recommended single dose in the UK is 200 mg - usually reduced for children, elderly and debilitating patients. 200mg lidocaine is present in 5g LIDIAM 4%w/w Cream for topical application.

Topically-applied local anaesthetics primarily target cell membranes on the absorption pathway as a function of the quantity applied, duration and area of dermal contact. Lidocaine is poorly absorbed through intact skin, reducing the potential for systemic side effects following topical administration. However, it still applies that longer application times prolong the anaesthetic duration. Absorption is higher through damaged skin, from mucous membranes and the gastro-intestinal tract, and rapid absorption is seen from injection sites, including muscle due to increased diffusion across more permeable membranes and increased vascularity. Increased absorption across the dermis may be enhanced by use of liposomes and application occlusion techniques.

Pharmacodynamic drug interactions
It is considered that the systemic additive effects will be minimal when combined with a topically applied lidocaine-based cream: administration of lidocaine with beta blockers and other anti-arythmics can cause additive cardio-depressant effects. This can also occur when lidocaine is given with i.v. phenytoin, although the long-term administration of phenytoin can lead to increased lidocaine dosages being required due to induction of drug-metabolising microsomal enzymes and an increase in plasma concentrations of the α1-acid glycoprotein.
IV.4 Clinical efficacy
The applicant has provided data in both requested indications. These are discussed below.

Venipuncture and cannulation
Study 31
This study assessed the comparative efficacy of Lidocaine 4% w/w Cream and EMLA in children undergoing venipuncture. This double-randomised, blinded crossover trial involved 120 children who were scheduled to have at least two venipunctures for non-study related reasons. Patients were randomised into one of two regimens: the 30 minute regimen in which each patient received 30 minute applications of Lidocaine 4% w/w Cream (no occlusion) and EMLA (under occlusion) in random order; or the 60 minute regimen in which each patient received 60 minute applications of both products, both under occlusion, in random order. The primary outcome measures were the child's rating of pain immediately after venipuncture using a 100mm visual analogue scale (VAS), and the parents' and blinded investigators observed behavioural distress scores. Both agents were effective in alleviating pain. There was no clinically or statistically significant difference in patient VAS scores within the 30 or 60 minute groups. There was also no clinical or statistical difference in VAS scores between the 30 minute Lidocaine 4% w/w Cream treatment without occlusion and the 60 minute EMLA treatment with occlusion. The parental and investigator's assessments using the behavioural distress scores were also clinically and statistically similar.

Study 32
This study investigated the anaesthetic equivalence of EMLA and Lidocaine 4% w/w Cream in children. Thirty healthy volunteers aged 7-13 years were randomised to have 2.5 g of EMLA applied to the right or left hand, under occlusion for 60 minutes. 2.5 g of Lidocaine 4% w/w Cream was applied without occlusion to the opposite hand for 30 minutes. Nurses, blinded to the randomisation, attempted to insert a 22-gauge needle into a vein in each hand. The subjects rated the pain on the Oucher scale and the nurses rated the difficulty of insertion. There was no significant difference between mean pain ratings; 20.5 for EMLA and 24.0 for Lidocaine 4% w/w Cream. There was also no significant difference in difficulty of vein cannulation. This study includes assessment by blinded investigators and consequently provides more robust evidence of the similarity between Lidocaine 4% w/w Cream applied for 30 minutes without occlusion and EMLA applied for 60 minutes with occlusion.

Study 35
A double-blind randomized controlled trial in children aged 1 month to 17 years was conducted. The trial sought to determine the success rate of cannulation, analgesic effectiveness, procedural duration and rate of adverse skin reactions when lidocaine 4% w/w cream is used before intravenous cannulation of children. 142 children took part which 69 of these received Lidocaine 4% w/w cream. Cannulation was achieved on first attempt in 74% of those children who received lidocaine compared with 55% of those who received the placebo. Among children 5 years old and over lower mean pain scores during cannulation were reported when using the Lidocaine 4% w/w cream. The total procedure duration was also shorter with use of the Lidocaine 4% w/w cream. Use of Lidocaine 4% w/w Cream was associated with a higher intravenous cannulation success rate, less pain, shorter total procedure time and minor dermal changes among children undergoing cannulation.

Study 41
This study compared the efficacy of Lidocaine 4% w/w Cream versus EMLA in reducing the pain associated with venipuncture in 43 adult platelet donors. In this double-blind study a pilot group of 12 patients were randomized to application times of 15 or 30 minutes, and application of Lidocaine 4% w/w Cream to the left or right arm with EMLA to the other. The mean of VAS scores for pain at 15 minutes and 30 minutes were 11.7 and 12.7 respectively. Accordingly the main study group of 31 patients were randomised to both products using left and right arms, but with a single application time of 15 minutes. For this group, the mean VAS score for Lidocaine 4% w/w Cream was 22.6 (SD 19.1) and for EMLA
was 21.8 (SD 16.5), a statistically insignificant difference (p=0.842). The subjects required two venipunctures and therefore provided the opportunity to compare venipuncture pain in the same individual at the same time with two anaesthetic agents. They experienced little discomfort with either drug, but only half of the patients felt they would prefer a local anaesthetic again.

**Study 5**
A double-blind, randomized, controlled, double-dummy trial of 330 healthy new-borns was conducted. Before venipuncture the neonates received 1 g of lidocaine cream topically or 2 mL of 24% sucrose solution or both. Sucrose was more effective than lidocaine for reducing pain during venipuncture in new-borns. The addition of lidocaine to sucrose did not confer any additional benefit to sucrose alone. There was no evidence of harm from lidocaine or sucrose.

**Study 46**
This study compared pain ratings in adults undergoing laser facial port-wine birthmark or tattoo removal. Seventy four patients were randomized to 4% lidocaine cream (Lidocaine 4% w/w Cream) applied without occlusion for 30 minutes or EMLA cream applied for 30 minutes with occlusion. Immediately after laser treatment, patients rated the degree of pain on a 100mm VAS. A blinded investigator assessed local cutaneous effects, difficulty of the procedure and behavioural distress. Four to eight weeks later patients were reassessed. There was no statistically significant difference between the two treatments in mean pain score (Lidocaine 4% w/w Cream =59.8, EMLA=69.2). Mean distress scores were higher in the EMLA group (4.05) than the Lidocaine 4% w/w Cream group (3.18).

The data provided above shows that lidocaine 4% cream is as effective as EMLA in venipuncture and cannulation in children.

The data provided in adults venipuncture and cannulation was less convincing as the only study presented showed no perceived benefit for either treatment and without a placebo arm, efficacy could not be confirmed. Therefore, the applicant provided evidence of the use of laser to simulate pain in comparative efficacy studies. This was accepted as moderately supportive.

**Venous cannulation in paediatrics <6years:**
A total of 6 x 4% liposomal lidocaine studies and bibliographic references presented include data from children <6 years, with total patients 462 patients plus 2 x EMLA studies in new-borns (total 51 patients).

The tables below provide a summary of efficacy studies to support the application.
<table>
<thead>
<tr>
<th>Reference Location of Study</th>
<th>Study Population Enrolled/Completed/Di scontinued Age range Mean age Gender</th>
<th>Study Type and Design Endpoint</th>
<th>Dosing regimen/Route</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>31 (Study 2 in PK)</strong></td>
<td>Children undergoing venepuncture 120 Age: 5y – 17y Mean Age: not specified Gender: 65M, 55F</td>
<td>Double randomized blinded crossover study Pain rating on VAS and investigator behavioural distress score.</td>
<td>Randomized to either (a) 30 min 2.5g E LA-Max no occlusion and 2.5g EMLA with occlusion or (b) 60 min E LA-Max 2.5g and EMLA 2.5g both under occlusion.</td>
<td>Both agents effective in alleviating pain. No clinical or statistical difference between 30 and 60 min groups. No statistical difference between 30 min non-occluded E LA-Max and 60 min occluded EMLA. Behavioural distress scores were clinically and statistically similar. Safety: 84% displayed no local reaction. In the E LA-Max groups, 2 had erythema, 11 local paresthesia, 1 pruritus, 1 skin discomfort.</td>
</tr>
<tr>
<td><strong>32</strong></td>
<td>Healthy child volunteers 30 Age range: 7y – 13y Mean age: 10.6y Gender: 14F, 16M</td>
<td>Randomized, investigator blind comparative study Comparative pain ratings on venepuncture</td>
<td>2.5g EMLA to L or R hand under occlusion for 60 mins, 2.5g of E LA-Max to opposite hand, no occlusion, for 30 mins. Venepuncture to each hand. Pain scored on the Oucher scale by subjects and difficulty of needle insertion rated by investigators.</td>
<td>No significant difference between mean pain ratings 20.0% for EMLA, 24.0% for E LA-Max. No significant difference in difficulty of vein cannulation between the 2 groups. Conclusion: EMLA under occlusion for 60 mins and E LA-Max with no occlusion for 30 min had similar anaesthetic efficacy. Mean-VAS scores for IV insertion were 25.7 (E LA-Max) and 26.8 (EMLA) p = 0.8 suggesting no significant difference in pain ratings between the two groups. Further evidence evidence of comparable efficacy of E LA-Max 30 mins vs EMLA 60 mins.</td>
</tr>
<tr>
<td><strong>33</strong></td>
<td>Children 60 Age range: 8y – 17y Mean age not specified Gender not specified</td>
<td>Randomised double-blind comparison study Comparative pain ratings on venepuncture</td>
<td>2.5g EMLA (60 mins) or 2.5g E LA-Max (30mins) applied to each hand with occlusion.</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
<th>Reference Location of Study</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>34</strong></td>
<td>Children 69 subjects Age range: 4y – 20.3y Mean age: 12.1y Gender not specified.</td>
<td>Randomised controlled trial Comparative pain ratings on peripheral intravenous catheter insertions.</td>
<td>Subcutaneous buffered 1% lidocaine or 2 5g topical E LA-Max applied during IV insertion with 22-gauge catheters.</td>
<td>VAS pain ratings were similar for both treatments (3.4 buffered lidocaine, 2.6 E LA-Max). Both anaesthetics provide comparable anaesthesia for IV insertion. Overall, use of Maxitane in 1m-17y ages was associated with a higher intravenous cannulation success rate, less pain, shorter total procedure time and minor dermal changes among children undergoing cannulation. Its routine use for painful cutaneous procedures should be considered whenever possible. Children aged 1m-17y showed a significantly lower increase in mean pain scores for cannulation compared with placebo.</td>
</tr>
<tr>
<td><strong>35 (Study 2 in Safety)</strong></td>
<td>Children 142 subjects Age range: 1m – 17y (31 lidocaine patients  aged &lt;5y) Mean age: 6.7y (lidocaine), 5.1y placebo) 79M, 63F</td>
<td>Phase IV double-blind randomized controlled trial Comparative pain ratings for IV insertions.</td>
<td>Patients treated with 4% local anaesthetic cream (Maxitane; E LA-Max) or placebo on 2 sites for 30min under occlusion.</td>
<td></td>
</tr>
<tr>
<td><strong>36</strong></td>
<td>Children 60 subjects (56 completed) Age range: 5y – 12y Mean age: 8.6y (amethocaine), 8.4y (lidocaine)</td>
<td>Prospective, randomised controlled trial Comparative pain ratings for venepuncture.</td>
<td>Patients treated with 1g 4% amethocaine or 1g 4% lidosomal lidocaine with occlusion for 30 mins.</td>
<td>Mean changes in pain ratings from baseline for the two groups were not statistically different. Also no statistical difference in cannulation difficulty and total cannulation attempts. 1g amethocaine &amp; 1g E LA-Max provide comparable analgesia for venepuncture in children. Excellent procedure outcomes were experienced by all patients without recurrent meatal stenosis. There was no significant difference between LMX4 and EMLA when applied 45 minutes before meatalotomy. When applied 30 minutes before meatalotomy LMX4 provided a significantly superior pain management than EMLA.</td>
</tr>
<tr>
<td><strong>37</strong></td>
<td>Children 52 subjects All male</td>
<td>Prospective randomized study</td>
<td>Topical anaesthetic application of LMX4 or EMLA prior to office meatalotomy.</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Study Population</td>
<td>Study Type and Design Endpoint</td>
<td>Dosing regimen/Route</td>
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</tr>
<tr>
<td>38</td>
<td>Healthy newborns</td>
<td>Comparative pain relief for circumcision.</td>
<td>Patients treated with 2g LMX4, 2g EMLA or 1% lidocaine Dorsal Penile Block prior to circumcision.</td>
<td>Infants receiving DPNB had higher mean HR and RR during circumcision than those treated with a topical cream. 1g dose of LMX4 was considered an effective anaesthetic for newborn males.</td>
</tr>
<tr>
<td>39 (Study 8 in PK)</td>
<td>Healthy newborns</td>
<td>Safety &amp; efficacy study</td>
<td>Patients treated with 1g EMLA or 1g placebo prior to circumcision.</td>
<td>Facial activity scores and facial activity measurements were lower during circumcision for the EMLA groups compared with placebo. EMLA successfully reduced the pain of circumcision compared with placebo.</td>
</tr>
<tr>
<td>40</td>
<td>Low birth weight infants.</td>
<td>Randomly assigned, blind study to assess pain relief for percutaneous venous central line insertion.</td>
<td>1-1.25g EMLA or placebo applied 1 hour before line insertion.</td>
<td>HR increased in placebo group, but not EMLA group. No signs of toxicity. EMLA was effective in relieving pain associated with line insertion.</td>
</tr>
<tr>
<td>41 (Study 1 in PK)</td>
<td>Volunteer adult platelet donors 43 subjects</td>
<td>Randomized, double blind, comparative study.</td>
<td>Patients randomized to 5g/16cm² LMX4 or EMLA on one arm and remaining drug to the other arm for 15 mins. No occlusion for either drug. Pain rated on VAS.</td>
<td>No clinically or statistically significant difference in VAS scores between EMLA and LMX4.</td>
</tr>
<tr>
<td>42</td>
<td>Adults 10 subjects</td>
<td>Comparative efficacy study using Eplug lasers to stimulate skin pain receptors.</td>
<td>LMX4 applied immediately prior to testing; EMLA applied 1.5h prior to testing with laser hair removal device.</td>
<td>LMX4 without occlusion showed anaesthesia after 20 mins in 7/10 subjects that was comparable to anaesthesia measured after 1-2h EMLA application times. This supports the proposed shorter application times for LM4 4% w/w Cream.</td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>43</td>
<td>Adult volunteers 20</td>
<td>Open uncontrolled study.</td>
<td>LMX4 applied to forearm under occluded and non-occluded conditions for durations ranging from 0-30 mins at 5 min intervals. Electrical stimulation of pain at 3 different frequencies stimulated 3 different sets of nociceptive fibres.</td>
<td>A different onset of cutaneous anaesthesia among the 3 frequencies was demonstrated. No significant difference in onset time of anaesthesia between occluded and non-occluded LMX4. Results suggested that painful stimuli such as venepuncture may be attenuated as early as 7 mins after application.</td>
</tr>
<tr>
<td>44</td>
<td>Adult volunteers 12</td>
<td>Comparative placebo controlled study.</td>
<td>LMX4, EMLA and tetracaine were statistically superior to placebo after 60 mins occlusion. 30 mins later all 4 agents were superior to placebo. LMX4 was significantly superior to betacaine-LA and tetracaine. EMLA was significantly better than betacaine-LA. Mean pain scores for all 4 agents after 30 mins were lower, but not significantly.</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Healthy adult volunteers 10</td>
<td>Comparative open study. Assessment of the relative onset of anaesthesia measured using a laser hair removal device using a Q-switched Nd:YAG laser to simulate pain.</td>
<td>EMLA applied under occlusion for 60 mins to one arm and LMX4 applied with no occlusion to 6 separate zones on the other. Every 5 mins LMX4 was removed from a zone and laser stimulated pain was applied. Pain scored immediately on VAS. Final zone scored 30 mins after application. Similar method with EMLA at 60 and 90 mins.</td>
<td>LMX4 displayed a significant linear decrease in pain over the 30 min. Comparison of each time value to control showed a significant decrease in pain starting 20 min. Mean first time to lowest pain score was 23.5 min. post application. EMLA showed significant decreases in pain at 60 and 90 mins. There was no significant difference between pain decrease by LMX4 at 30 mins and EMLA at 60 mins. i.e. LMX4 at 30 mins provides analgesia comparable to that achieved with EMLA after 60 mins.</td>
</tr>
</tbody>
</table>
Surface Anaesthesia (larger surface areas)
Surface Anaesthesia prior to administration of painful topical treatments on larger surface areas:

Study 51
This study investigated the efficacy of identical doses of EMLA versus Lidocaine 4% w/w Cream for pain relief during a 70% unbuffered glycolic acid (GA) - 35% trichloroacetic acid (TCA) medium depth chemical peeling of selected areas of the faces of ten patients aged between 18 to 70 years. The topical anaesthetic was applied for 30 minutes without occlusion. A 10 point numerical scale was used to rate the pain felt at three stages during the procedure. Both topical anaesthetics were found to substantially decrease the discomfort felt during the chemical peeling process compared to placebo, with ratings of 2.45 and 2.25 for EMLA and Lidocaine 4% w/w Cream compared to 9.40 for placebo.

Study 52
This study investigated the relative efficacy and onset of action of Lidocaine 4% w/w Cream versus EMLA in 10 adults using a laser hair removal device. EMLA was applied to the forearm (the exact dose was not specified but was assumed to be the current approved EMLA dosage of 1.5g-2g EMLA/10cm²) for 1.5 hours without occlusion prior to Epilight high-energy light source pulsing, whereas Lidocaine 4% w/w Cream was applied immediately prior to testing. The authors found that Lidocaine 4% w/w Cream without occlusion provided good topical anaesthesia with much faster onset of action than the 1-2 hours recommended for EMLA, and maximum pain relief was achieved in 7 out of 10 subjects just 20 minutes after Lidocaine 4% w/w Cream application.

Study 53
This study has demonstrated comparable anaesthetic efficacy of Lidocaine 4% w/w Cream and EMLA when applied under occlusion for 30 minutes prior to electrodesiccation of epidermal dermatosis papulosa nigra (DPN). Forty subjects, each with between 5 to 40 hyperpigmented papules on the face and/or neck, were randomised and treated with a study drug. The average area treated was roughly 40cm², divided evenly between two sides of the body (giving a 20cm² area of skin on each arm. In >80% of cases, treatment was on the face. Histologically, DPN only involve the epidermis, so the authors note that deep anaesthesia is not required for this indication, thus the study drug was applied in a layer approximately 1 to 2 mm thick. Approximately 6.8 g of each study drug was applied in total over the 40cm² (equivalent to 1g/6cm²) and it was removed after 30 minutes after which time an initial two or three DPN were removed. Subjects were then asked if they required an additional 30 minute treatment of anaesthetic prior to removal of all of the targeted lesions. Subjects were asked to rate the discomfort
of the electrodesiccation after the first and second 30 minute applications of study drug as applicable. An 11-point numeric scale was used. The authors concluded that EMLA and Lidocaine 4% w/w Cream both provide satisfactory levels of anaesthesia for electrodesiccation of DPN when applied at the stated dosage under occlusion for 30 minutes.

In the other studies, mostly in smaller areas and for cosmetic procedures, efficacy has been shown to be comparable to EMLA and better than placebo.

The Applicant presented a comprehensive general discussion of the safety and efficacy of topical lidocaine 4% in large surface areas. The following studies were submitted: 4 x 4% liposomal lidocaine studies totalling 81 patients (studies 22, 23, 24 and 25 – Table 2) and 2 EMLA studies totalling 367 patients were presented covering areas up to 300cm². Surface anaesthesia of the skin prior to a range of cosmetic procedures up to 300cm² include laser hair removal, facial chemical peels, DPN electrodesiccation, pinprick pain and facial laser resurfacing as examples.

Table 4
Summaries of efficacy studies of LMX4 and similar lidocaine formulations – Large Surface Area Procedures

<table>
<thead>
<tr>
<th>Reference Location of Study</th>
<th>Study Population Enrolled/Completed/Discontinued Age range Mean age Gender</th>
<th>Study Type and Design Endpoint</th>
<th>Dosing regimen/Route</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 (Study 71 in Safety)</td>
<td>Adult volunteers 12 Age not specified Mean age 36y Gender 5F, 7M</td>
<td>Comparative placebo controlled study Degree and duration of anaesthesia for pain simulated using Nd:YAG laser techniques typically used for laser hair removal</td>
<td>Equal amounts (0.2ml) of EMLA, LMX4, 4% tetracaine cream, betacaine-LA ointment and placebo applied to 10 test sites on the forearm under occlusion for 60 minutes. Degree of anaesthesia assessed by laser stimulation immediately and 30 minutes following occlusion.</td>
<td>LMX4, EMLA and tetracaine were statistically superior to placebo after 60 mins occlusion. 30 mins later all 4 agents were superior to placebo. LMX4 was significantly superior to betacaine-LA and tetracaine. EMLA was significantly better than betacaine-LA. Mean pain scores for all 4 agents after 30 mins were lower, but not significantly, indicating that anaesthesia continues after the cream has been removed.</td>
</tr>
<tr>
<td>50 (Study 74)</td>
<td>Adults 40 patients 19-59y (mean 30y)</td>
<td>Monocentric, randomised double blind intra-individual companion efficacy study</td>
<td>2g/16cm² LMX4, EMLA or placebo applied for 30 mins (20 subjects) or 60 mins (20 subjects).</td>
<td>LMX4 and EMLA gave comparable efficacy after 30 mins for pain reduction associated with pin pricks. Pain reduction continued for a further 90 minus following cream removal.</td>
</tr>
<tr>
<td>51</td>
<td>Patients undergoing facial peels 10 16y – 70y Mean age 36y Gender 5F, 7M</td>
<td>Comparative placebo controlled study Degree and duration of anaesthesia produced for medium depth chemical peeling.</td>
<td>Faces coated with 70% glycolic acid diluted with water after 2 mins. Then sequential application of EMLA, LMX4 and placebo to selected areas of the face for 30 mins with no occlusion. Then removal of creams and application of TCA peel.</td>
<td>Statistically significant decrease in pain felt during the peel with both topical anaesthetics compared to placebo. No significant difference in efficacy between EMLA and LMX4. Histology: 48hrs and 90 days post-peel was equivalent in all 3 groups.</td>
</tr>
</tbody>
</table>
IV.5 Clinical safety
The applicant has presented the safety data summarised for each of the requested indications. This is from the studies presented in the efficacy section above as well as in use data.

Although the parenteral administration of lidocaine can be associated with significant cardiac and central nervous system (CNS) toxicity, the plasma levels of lidocaine attained following recommended topical administration of a 4% lidocaine cream are well below those associated with systemic toxicity.
Surface Anaesthesia prior to Venous Cannulation or Venepuncture

Studies

A study gathered data from a total of 76 patients involved in their comparative clinical trial. Ten patients in the Lidocaine 4% w/w Cream group (26.3%) had at least one adverse event compared to 18 patients in the EMLA group (47.4%). The difference approached statistical significance (p= 0.0571). At least 10% of the total patients reported redness, itching, blistering, pallor, and/or sensitivity. Only one adverse event in the Lidocaine 4% w/w Cream group (pallor) was considered to be probably related to treatment compared to seven events in the EMLA group. All remaining adverse events in both treatment groups were considered to be unrelated to treatment.

A study reported four adverse events in this comparative study on 43 adults. Three were not related to drug. The fourth was an intravenous (IV) infiltration that was thought to be possibly related to drug.

A comparative study of four topical anaesthetics an occasional side effect of blanching or erythema at the site of application was reported. This effect resolved within two hours.

A comparative study involving 120 children with no skin reactions of any type at the treatment site were observed in >84% of subjects. In the Lidocaine 4% w/w Cream group of patients, following 30 minutes application without occlusion, there was one report of erythema, four reports of pallor, one report of pruritus, and no reports of skin discomfort; following 60 minutes application with occlusion, there was one report of erythema, seven reports of pallor, no reports of pruritus and one report of skin discomfort. There were no statistically significant differences in skin reactions to either study medication at the 30 minute or 60 minute application times. However, more than twice the incidence of pallor was observed in patients who were treated with EMLA for 60 minutes with occlusion (n=9) than in patients treated with Lidocaine 4% w/w Cream for 30 minutes without occlusion (n=4).

The rate of adverse events in the small exposure venepuncture indication is low and benign. No real systemic adverse events are reported and in use data shows a low event rate.

Surface Anaesthesia prior to administration of painful topical treatments on larger surface areas

In a study, a 5g dose of Lidocaine 4% w/w Cream was applied to 50cm² of the arm once a day for three days. The product was not actively removed from the skin between applications. EMLA was used as the reference product, and was only administered on day one of the treatment period. The reported adverse events following Lidocaine 4% w/w Cream application during all 3 days of the study are summarised in Table below:

Table 5
Possible relationship of adverse events with study drug following 5g/50cm² Lidocaine 4% w/w Cream application

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Mild</th>
<th>Moderate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related, unlikely related</td>
<td>Possibly related</td>
<td>Not related, unlikely related</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Erythema at treatment site</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pin in right knee</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

A study investigated the safety of occluded Lidocaine 4% w/w Cream in 8 patients at a dosage of 1g/10cm² on surface areas up to 600cm². Test subjects were evaluated clinically for neurological side effects of lidocaine including tremor, nystagmus, drowsiness, agitation, light headedness, dysarthria, slurred speech, hallucinations, emotional lability and memory impairment. They were also monitored.
for cardiovascular effects, such as bradycardia and hypotension, and gastrointestinal complaints, including nausea, vomiting and anorexia. Clinically, none of the test subjects exhibited any of these symptoms during the trial and the use of Lidocaine 4%/w/w Cream at the dosage of 1g/10cm² with 60 minute application times was considered to be locally safe.

A study to evaluate the potential of Lidocaine 4%/w/w Cream to induce allergic contact dermatitis by nine 48 hour repetitive patch applications to this skin was conducted. Four test articles and associated vehicles, including Lidocaine 4%/w/w Cream and lidocaine 5% cream were tested at a dosage of approximately 0.2 ml/1cm² on a total of 217 healthy volunteers aged between 18 to 70 years. Water was used as a negative control and 0.1% sodium lauryl sulphate was used as a positive control. Each volunteer received nine applications of approximately 48 hours of each of the test articles over a three week period. The application sites were inspected at 48 hour intervals after each application. After the three week period, volunteers rested for 14-17 days and then each test article was applied to a new site for 48 hours and evaluated after 48 and 96 hours. Two subjects exhibited reactions to 5% lidocaine and one to Lidocaine 4%/w/w Cream, which were possibly indicative of allergic contact dermatitis. Each of these subjects was re-challenged. All three subjects exhibited mild adverse reactions of either erythema, oedema, papules or peeling. In this study out of 217 healthy volunteers, only one subject exposed to Lidocaine 4%/w/w Cream exhibited signs of allergic contact dermatitis, even with repetitive 48 hour application times.

The other studies presented are generally using much smaller quantities but the rates of adverse events attributable to lidocaine are small or non-existent. Allergic sequelae have been shown to have a low rate and be relatively benign.

No serious spontaneous adverse drug reactions have been received. 14 non-serious spontaneous adverse drug reactions were reported, 12 of which were reported by a healthcare professional. No incidents of drug interactions, overdose or abuse were reported. Nine cases related to a lack of efficacy and six cases related to allergic reactions. There was one case of medication error (difficulty inserting the cannulation after application of the product). Overall the reaction rate is considered to be very low.

In addition to the above studies the Applicant provided evidence of the PK safety of the proposed 1.5g-2g/10cm² dosage to support the upper surface area limit of 300cm² in adults. 4 x 4% liposomal lidocaine studies totalling 81 adult patients and 2 EMLA studies totalling 367 adult patients are presented covering areas up to 300cm² skin, measuring serum levels of lidocaine and major metabolite monoethylglycinexylidide (MEGX). Subjects were also evaluated for neurological side effects such as tremor, nystagmus, drowsiness, agitation, light-headedness, dysarthria, slurred speech, hallucinations, emotional lability and memory impairment.

The Applicant has also provided additional studies as evidence for paediatric PK and local safety. One of these studies (12 x 2-5 year olds using ELA-Max) was considered as own/unpublished data and is accepted. The other references were considered as supporting data. Calculations, based upon another PK study for the <12months paediatric dosage regimens, supported the systemic safety of Lidocaine 4%/w/w Cream when applied topically at the dosages proposed for paediatrics aged 1 month and older. The safety of the proposed venous cannulation and venepuncture maximum 4 hour application time in the 3-12 month age group was supported by the study findings.
Table 6 - Safety studies of LMX4 and similar lidocaine formulations – all proposed indications

<table>
<thead>
<tr>
<th>Reference Location of Study</th>
<th>Study Population Enrolled/Completed/Di scontinued Age range Mean age Gender</th>
<th>Study Type and Design Endpoint</th>
<th>Dosing regimen/Route</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>Newborns 330 subjects (mean gestational age 39.5 weeks)</td>
<td>Double-blind randomised, controlled, double-dummy trial comparing the efficacy of ELA-Max vs sucrose for relieving venepuncture pain.</td>
<td>1g ELA-Max, 24% sucrose solution or a combination of both was applied to the hand for 30 or 40 minutes with occlusion.</td>
<td>No clinically significant AEs reported for the ELA-Max group. Splitting-up was the only AE noted, and there was no significant difference in the incidence rate between the liposomal lidocaine and sucrose groups (1.4% &amp; 2.7% respectively, p=0.22).</td>
</tr>
<tr>
<td>62</td>
<td>Children 1m–17y 142 subjects (69 lidocaine, 31 &lt;5y)</td>
<td>Phase IV randomised controlled efficacy study comparing 4% liposomal lidocaine with placebo (vehicle cream with no active).</td>
<td>1g cream applied to 2.5cm² area on the hand with occlusion for 30 mins.</td>
<td>No significant difference in the adverse events recorded for the study drug &amp; placebo. All local adverse events were mild and were attributed to hydration of the skin from occlusion and were not clinically significant.</td>
</tr>
<tr>
<td>63 (Study 3 in PK)</td>
<td>Children 12 subjects 2y–5y Mean age 4.21 Gender not specified</td>
<td>Open study investigating safety of 3g/6.25cm² ELA-Max dose.</td>
<td>Single 30 min application 3g of ELA-Max or 60 min application of EMLA to a 2x2 inch area of the arm.</td>
<td>Two subjects in the ELA-Max group reported a total of 3 AEs that were all mild and related to the digestive system. ELA-Max and EMLA used in the study were considered to be well tolerated.</td>
</tr>
<tr>
<td>64</td>
<td>Children 60 subjects (66 completed) Age range: 5y–12y Mean age: 9.6y (lidocaine), 8.4y (amethocaine)</td>
<td>Prospective, randomised controlled trial. Comparative pain ratings for venepuncture.</td>
<td>Patients treated with 1g 4% amethocaine or 1g 4% liposomal lidocaine with occlusion for 30 mins.</td>
<td>The frequency of adverse skin reactions was low and was not significant between groups. The amethocaine group exhibited a higher incidence of erythema than the lidocaine group.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference Location of Study</th>
<th>Study Population Enrolled/Completed/Di scontinued Age range Mean age Gender</th>
<th>Study Type and Design Endpoint</th>
<th>Dosing regimen/Route</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 (Study 2 in PK)</td>
<td>Children 120 subjects 5y-17y</td>
<td>Double-blinded random cross-over efficacy study.</td>
<td>2.5g/6.25cm² LMX4 or EMLA applied for 30min (no occlusion) or 60min (occluded)</td>
<td>LMX4 30 min 89.9% no reaction; LMX4 60 min 84.5% no reaction.</td>
</tr>
<tr>
<td>66 (Study 4 in PK)</td>
<td>Healthy volunteer children 15 subjects (12M/3F) Age range: 12-18 y Mean age: 14.60</td>
<td>Liposomal lidocaine PK study.</td>
<td>1 single 30 min application of 3g 5% liposomal lidocaine cream to 25cm² area of the forearm.</td>
<td>Patient’s vital signs changed in some subjects up to 24h post-application, but were considered unlikely related to the study medication. All AEs reported in the study were non-serious and mild. Most were considered unrelated to the study medication and all resolved during follow-up.</td>
</tr>
<tr>
<td>67</td>
<td>Healthy adults 217 patients 18y–70y</td>
<td>Safety study.</td>
<td>4thh repetitive patch application to skin investigating the potential of topical anaesthetics(5) including ELA-Max to induce allergic contact dermatitis. 0.2ml of each test article applied 9 times to patch sites over 3 weeks.</td>
<td>Only 1/217 patients exhibited allergic contact dermatitis. At the 4th evaluation 18/4 of the subjects had no visible reaction to the ELA-Max applications. At the 9th evaluation 210 patients scored 0 for ELA-Max. Very low overall incidence of topical reactions following repeated ELA-Max applications.</td>
</tr>
<tr>
<td>68</td>
<td>Adults 74 subjects Age: not specified Mean age: 31.4 (LMX4) 30.8 (EMLA) Gender: 24M, 52F</td>
<td>Comparative randomised, investigator blind study.</td>
<td>Patients randomised to LMX4 non-occluded for 30 mins or EMLA occluded for 30 mins. Pain rated on VAS immediately after treatment. Investigator assessed local cutaneous effects and behavioural distress.</td>
<td>Safety: 10 (26.3%) of LMX4 patients had at least one adverse event. 10% of all patients had redness, itching, blistering, paller sensitivity. Only one of these (patient) was thought to be related to LMX4.</td>
</tr>
<tr>
<td>Reference</td>
<td>Location of Study</td>
<td>Study Population</td>
<td>Study Type and Design Endpoint</td>
<td>Dosing regimen/Route</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td>------------------</td>
<td>--------------------------------</td>
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</tr>
<tr>
<td>69</td>
<td>(Study 1 in PK)</td>
<td>Volunteer adult platelet donors 43 subjects Age: not specified Mean age: not specified Gender: not specified</td>
<td>Randomized, double blind, comparative study. Degree of anaesthesia recorded</td>
<td>Patients randomized to 5g/15cm² LMX4 or EMLA on one arm and remaining drug to the other arm for 15 mins. No occlusion for either drug. Pain rated on VAS. Serum lidocaine levels measured in 10 patients.</td>
</tr>
<tr>
<td>70</td>
<td>(Study 5 in PK)</td>
<td>Newborns 330 subjects (mean gestational age 39.16 weeks)</td>
<td>Double-blind randomised, controlled, double-dummy trial comparing the efficacy of ELA-Max vs sucrose for relieving venepuncture pain.</td>
<td>1g ELA-max; 24% sucrose solution or a combination of both was applied to the hand for 30 or 40 minutes with occlusion.</td>
</tr>
<tr>
<td>71</td>
<td></td>
<td>Adult volunteers 12 Age: not specified Mean age: 35y Gender: 5F, 7M</td>
<td>Comparative placebo controlled study Degree and duration of anaesthesia produced.</td>
<td>Equal amounts (0.2ml) of EMLA, LMX4, 4% lignocaine cream, betacaine-LA ointment and placebo applied to 10 test sites on the forearm under occlusion for 60 minutes. Degree of anaesthesia assessed by laser stimulation immediately and 30 minutes following occlusion.</td>
</tr>
<tr>
<td>72</td>
<td>(Study 6 in PK)</td>
<td>Healthy adults 24 (5 F, 19 M) 22y – 54y</td>
<td>Single and multiple dose pharmacokinetic study.</td>
<td>24 Healthy subjects received a single treatment of 5g EMLA (reference) and three treatments of 5g LMX4/50cm² (test) over 1 or 3 consecutive days (test reference treatments separated by 7 days and not actively removed in between).</td>
</tr>
</tbody>
</table>

**IV.6 Risk Management Plan (RMP)**

The Marketing Authorisation Holder (MAH) has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lidocaine 4% w/w Cream.
Table 7
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity including</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>anaphylactic shock</td>
<td>/ patient information leaflet.</td>
<td></td>
</tr>
<tr>
<td>Severe corneal irritation after accidental eye exposure</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large dose toxicity</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat use toxicity</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interaction with Class I anti-arrhythmic drugs</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interaction with drugs that reduce the clearance of lidocaine when</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>lidocaine is given in high doses over a long period of time</td>
<td>/ patient information leaflet.</td>
<td></td>
</tr>
<tr>
<td>Drug interaction with other local anaesthetics when lidocaine is given in</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>large doses</td>
<td>/ patient information leaflet.</td>
<td></td>
</tr>
<tr>
<td>Patients treated with Class III anti-arrhythmic drugs</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ototoxicity (when administered in middle ear)</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in patients with hepatic impairment</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross sensitivity with para-aminobenzolic acid derivatives</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with live vaccines</td>
<td>Inclusion in SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Use in children under 1 month</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in paediatric population on larger surface areas of intact skin</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use over raw or blistered areas</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in pregnancy</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on fertility</td>
<td>Inclusion in SmPC, and labelling</td>
<td>None</td>
</tr>
<tr>
<td>/ patient information leaflet.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of risk minimisation measures
Routine risk minimisation is provided through the SmPC and the patient information leaflet. No additional risk minimisation measures are planned for this product.

IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.
V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to LMX4 (Ferndale Pharmaceuticals Ltd). The bridging report submitted by the applicant is acceptable.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION
The applicant has provided a mixed dossier application in support of the quality, efficacy and safety of this product. The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with lidocaine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

### Labelling

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRINTED TUBE 5g or 30g</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Lidocaine 4% w/w Cream

   Lidocaine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   1 gram of cream contains 40mg of lidocaine

3. **LIST OF EXCIPIENTS**

   Benzyl Alcohol, Carbomers, Cholesterol, Hydrogenated Soy Lecithin, Polysorbate 80, Propylene Glycol, Trolamine, all-rac-alpha-Tocopherol Acetate. Purified Water

   See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Cream
   5g or 30g e

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For cutaneous use:
   Read the package leaflet before use or use as directed by a medical practitioner.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

   Keep out of the sight & reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

   Avoid contact with the eyes

8. **EXPIRY DATE**

   MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

   Do not freeze. After opening use within 6 months.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>12. MARKETING AUTHORISATION NUMBER(S)</td>
<td>PL20685/0038</td>
</tr>
<tr>
<td>13. BATCH NUMBER</td>
<td>XXXXXX</td>
</tr>
<tr>
<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
<td>P</td>
</tr>
<tr>
<td>15. INSTRUCTIONS ON USE</td>
<td></td>
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</tbody>
</table>
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
5g tube minimum particulars

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lidocaine 4% w/w Cream
Lidocaine

2. METHOD OF ADMINISTRATION

For cutaneous use:
Read the package leaflet before use or use as directed by a medical practitioner.

3. EXPIRY DATE

MM/YYYY

4. BATCH NUMBER

XXXXXX

5. OTHER

5g c
After opening use within 6 months.
MAH logo
Keep out of the sight & reach of children.
Avoid contact with the eyes.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 5g, 30g, 5 x 5g, 1x 5g plus 2 occlusive dressings, 5 x 5g plus 10 occlusive dressings

1. NAME OF THE MEDICINAL PRODUCT

Lidocaine 4% w/w Cream
Lidocaine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 gram of cream contains 40mg of lidocaine

3. LIST OF EXCIPIENTS

Benzyl Alcohol, Carbomers, Cholesterol, Hydrogenated Soy Lecithin, Polysorbate 80, Propylene Glycol, Trolamine, all-ara-a-Tocopheryl Acetate, Purified Water
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Cream
<5g e>
<5 x 5g e>
<5g plus 2 occlusive dressings e>
<5 x 5g plus 10 occlusive dressings e>
<30g e>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For cutaneous use:
Read the package leaflet before use or as directed by a medical practitioner.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight & reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid contact with the eyes

8. EXPIRY DATE

MM/YYYY
9. SPECIAL STORAGE CONDITIONS

Do not freeze. After opening use within 6 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferndale Pharmaceuticals Ltd. Wetherby, LS23 7FX, UK.

12. MARKETING AUTHORISATION NUMBER(S)

PL20685/0038

13. BATCH NUMBER

XXXXXXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

For use as a local anaesthetic to produce numbness of the skin for temporary relief of pain associated with venous cannulation, venipuncture, and painful topical treatments over larger areas of intact skin.

16. INFORMATION IN BRAILLE

Lidocaine 4% w/w
# Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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