LMX 4 LIDOCAINE 4% W/W CREAM

PL 20685/0034

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ferndale Pharmaceuticals Ltd a Marketing Authorisation (licence) for the medicinal product LMX 4 Lidocaine 4%w/w Cream (Product Licence number: 20685/0034).

This cream is applied to the skin before a needle is inserted into a vein for medical purposes, giving pain relief.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking LMX 4 Lidocaine 4%w/w Cream outweigh the risks, hence a Marketing Authorisation has been granted.
LMX 4 LIDOCAINE 4% W/W CREAM

PL 20685/0034

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product LMX 4 Lidocaine 4%w/w Cream (PL 20685/0034) to Ferndale Pharmaceuticals Ltd on 20 November 2007. This medicinal product is available from pharmacies.

This complex abridged application for LMX 4 Lidocaine 4%w/w Cream was submitted as a bibliographical application in accordance with article 10a of Directive 2001/83/EEC.

This product contains lidocaine and is used as a local anaesthetic for topical use to produce surface anaesthesia of the skin prior to venous cannulation or venipuncture.
PHARMACEUTICAL ASSESSMENT REPORT

ACTIVE SUBSTANCE

Lidocaine

INN: Lidocaine
Chemical name: 2-diethylaminoaceto-2’,6’-xylidide
Compendial name: Lidocaine
CAS registry code: CAS: 137-58-6
Molecular formula: C_{14}H_{22}N_{2}O,
Molecular weight: 234.3
Physical form: A white or almost white, crystalline powder,

![Molecular structure of Lidocaine]

Appearance: white or almost white powder
Melting temperature: 66 to 69 °C
Solubility: Practically insoluble in water, very soluble in alcohol and in methylene chloride, freely soluble in ether.
Crystallinity: crystalline

A Certificate of Suitability has been provided, it indicates that the manufacturing process and process controls are acceptable.

The range of tests and the limits in the active substance specification are in line with the Ph. Eur monograph.

Since the analytical methods used are standard and are in the Ph. Eur. monograph, they are considered to be validated.

Certificates of Analysis for batches of drug substance have been provided and show compliance to the specification.

It is stated that pharmacopoeial reference standards are used. This is accepted.

The drug substance is stored in suitable packaging.

Stability information has been provided. It is stated that, based on the results of the stability program, the proposed shelf life for the drug substance is 5 years when suitably packaged. The storage condition is ‘Store below 25°C’.
DRUG PRODUCT

Description and composition of the drug product
The cream contains the following ingredients: lidocaine, benzyl alcohol, carbomer 940, cholesterol, phospholipids, polysorbate 80, propylene glycol, trolamine, vitamin E acetate and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of phospholipon 80H (in the absence of a Ph Eur monograph, this is acceptable). Satisfactory certificates of analysis have been provided for all excipients.

The applicant has stated that the excipients cholesterol and polysorbate 80 are of human or animal origin. Satisfactory TSE Certificates of Suitability have been provided for these excipients.

No overages are used.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on finished product batches. The results are satisfactory.

Finished product specification
The Finished Product Specification is in line with the Ph. Eur. requirements for topical semi-solid preparations and is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container closure system
The pack size is 5g and comprises of an aluminium tube with an epoxyphenolic internal lacquer and fitted with a polypropylene cap. 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.

Specifications and Certificates of Analysis for all packaging types have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.
**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of two years when the product container is unopened and of 3 months once the container is opened are satisfactory when the storage precaution “do not store above 25°C” is followed.

**CONCLUSION**
A product license may be granted for this product.
NON-CLINICAL ASSESSMENT

INTRODUCTION
This is an application for LMX 4 Lido caine 4% w/w cream, which is a topical anaesthetic containing 4% lidocaine in a liposome base. The use of topical local anaesthesia is well established. It is used for pain relief associated with skin procedures such as laser pulses, surgical procedures or soft tissue augmentation.

Topically applied anaesthetics prevent the initiation and transmission of nerve impulses and provide cutaneous analgesia by acting on free nerve endings in the dermis. Specifically, they block nerve impulse conduction by interfering with voltage dependent sodium channels. By inhibiting sodium influx, the threshold for nerve excitation increases and finally the ability to generate an action potential is lost. EMLA, an eutectic mixture of 2.5% lidocaine and 2.5% prilocaine in an oil-in-water emulsion cream, is the most widely used topical anaesthetic. The onset of action is after 30 to 60 minutes and it is commonly used under occlusion.

Lidocaine is a compound with long clinical experience. This cream formulation includes phospholipon 80 (soy bean lecithin) that forms multilamellar vesicles containing several lipid bilayers (liposomes) dispersed in an aqueous medium. The lipid bilayers are stated to be able to enclose the water insoluble active ingredient and to stabilise the formulation. They are stated to facilitate the penetration of lidocaine into the skin, carrying the encapsulated drug into the dermis and providing a sustained release. They are also stated to protect the anaesthetic from metabolic degradation, allowing prolonged duration of action. A layer of fatty, subcutaneous tissue with poor blood flow extends into the bottom of the dermis. The sequestration of lidocaine in fat cells is stated to slow the rate of absorption and reduce the peak plasma level and also the risk of toxicity.

GLP ASPECTS
The non-clinical overview makes reference to relevant non-clinical and clinical data. Many of the studies were performed in the days when the principles and guidelines of GLP had not yet been established.

NON-CLINICAL ASPECTS
The pharmaco-toxicology of lidocaine is well known and no new studies have been conducted. The product is a formulation containing liposomes. The use of liposomes is established. There are at least two currently authorised products: Myocet Infusion (EM 14188/0004), which has a European MA, and Daunoxome Infusion (PL 16807/0002), which has a UK national licence.

The local tolerance of the formulation was investigated in a single 24 hour patch test to the abraded and unabraded skin of New Zealand white rabbits. The formulation was only slightly irritant.

NON-CLINICAL OVERVIEW
The non-clinical overview is a summary of some the published literature on the nonclinical and clinical aspects of lidocaine. In addition, a report of a study reported in 2002 on the local tolerance of the formulation is included.

SUMMARY OF PRODUCT CHARACTERISTICS
Section 5.3 (Non-clinical Safety Data) is acceptable.

CONCLUSIONS
This application is acceptable from a non-clinical point of view.
INTRODUCTION
Indications
“Local anaesthetic for topical use to produce surface anaesthesia of the skin prior to venous cannulation or venipuncture.”

Assessor’s comment:
These indications are satisfactory

Posology & method of administration
“Adults, including elderly, and children over one month of age.
Apply 1g to 2.5g of cream onto the skin to cover a 2.5cm x 2.5cm (6.25cm²) area where venous cannulation or venipuncture will occur. No more than 1g of cream should be applied to infants below the age of 1 year. 1g of cream equates to approximately 5cm of cream squeezed from the tube.

The cream should remain undisturbed and the area can be covered with an occlusive dressing to prevent disturbance or interference by the patient or other external factors. Adequate anaesthesia should be obtained after 30 minutes at which time the LMX 4 Cream should be removed using a clean gauze swab and the site for venous cannulation or venipuncture prepared in the usual manner. The procedure should be initiated approximately 5 minutes after the cream has been removed. Maximum application time should not exceed 60 minutes.”

Assessor’s comment:
This is satisfactory.

CLINICAL PHARMACOLOGY
Pharmacokinetics
The PK characteristics of various formulations of lidocaine are well documented in the literature. The main PK/safety issue with regard to LMX 4 Lidocaine 4%w/w Cream was whether there is any new risk of clinically relevant systemic absorption of lidocaine from this liposomal-based formulation.

To address this, the applicant detailed a single and multiple dose pharmacokinetic study using two formulations of lidocaine undertaken in 24 healthy male or female subjects. This open, single/multiple dose, two-way, randomized crossover study was conducted with a washout period of a minimum of 7 days between two treatments.

In this study, 5 grams of LMX 4 Lidocaine 4% w/w Cream (the test formulation) or registered topical lidocaine/prilocaine formulation (EMLA®, the reference formulation) were applied to the arm. Both formulations were compared, based on rate and extent of absorption of lidocaine and metabolite from the formulations, respectively. In addition, both formulations were compared descriptively with regard to the local and systemic tolerability and local erythema assessments by means of an automated device (chromameter).
The results of this study showed that the pharmacokinetic profile of the two topical formulations of lidocaine, based on determination of the rate and extent of absorption of lidocaine from the lidocaine topical formulations, were comparable.

From the study it was also concluded that the test and reference treatments were well tolerated in all 24 subjects and no clinically significant changes were noted. No serious adverse events were reported. A total of eight adverse events (six mild and 2 moderate) were reported by seven (29.2%) subjects. The relationship to study drug of three adverse events was judged as “not related”, for four adverse events the relationship to study drug was judged as “unlikely related” and for one adverse event as “possible related”.

All evaluations at screening and at the end of study revealed no clinically significant abnormalities and physical examinations did not reveal any change from baseline to end of study assessments.

The local tolerability assessment showed a good tolerability for both formulations, with no observations of local irritation of a grade higher than 1 (erythema) in the ICDRG scale and at least 70% of subjects showed no irritation at each assessment point.

The applicant has provided details of two further studies examining the safety of liposomal lidocaine cream, these provide further assurance of the safety of the treatment.

**Pharmacodynamics**
This aspect has been fully described in the literature and summarised in the dossier.

**CLINICAL EFFICACY**
The applicant has conducted a randomised, double-blind, placebo-controlled trial comparing LMX 4 Lidocaine 4% w/w Cream to placebo.

There were 151 patients randomised into the trial. One gram of the proposed product or placebo cream (the base cream without the active) with occlusion was applied for 30 minutes to an approximately 2.5cm² of each hand.

The study report notes that this corresponds to approximately 0.16g/cm² per hand, which complies with the proposed usage of the product. Both hands were treated to give the nurse the choice of the best hand for cannulation.

**Patient accountability**
There were 151 patients randomised into the trial, but nine patients dropped out before cannulation took place. For five of these patients their clinical condition had improved and i/v cannulation was no longer considered necessary, one patient wiped off the cream through excessive movement, one patient withdrew, in one patient the cream was accidently removed prematurely, and in the final patient the cream was deliberately removed prematurely to allow a separate investigation to take place.

It seems reasonable to exclude such patients from the analysis.
Pain was measured using the Faces Pain Scale Revised (FPS-R), with scores ranging from zero (no pain) to five (worst possible pain). The scores were evaluated by three different raters:

1. Pain assessment by the child – this was done only in children ≥5 years of age.
2. Pain assessment by the parents – this was planned for all patients, but the assessment was missing for 4 patients on LMX 4 Lidocaine 4% w/w Cream and 6 patients on placebo.
3. Pain assessment by research assistant – assessments were available for all patients.

Pain scores were measured during the first cannulation attempt for each child. Baseline measurements (pain without provocation) were taken 5 minutes before the cream was removed. The primary analysis of pain was pain during cannulation minus the baseline score. The scores from the three different raters were given equal priority.

### Mean (sd) FPS-R scores

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.3 (1.2)</td>
<td>1.6 (1.6)</td>
<td>p=0.29</td>
</tr>
<tr>
<td>At cannulation</td>
<td>2.6 (1.5)</td>
<td>3.9 (1.5)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.3 (1.3)</td>
<td>2.3 (1.6)</td>
<td>p=0.01</td>
</tr>
<tr>
<td><strong>Parents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.2 (1.2)</td>
<td>1.3 (1.2)</td>
<td>p=0.695</td>
</tr>
<tr>
<td>At cannulation</td>
<td>2.7 (1.5)</td>
<td>3.6 (1.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.5 (1.3)</td>
<td>2.3 (1.2)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Research assistant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.1 (1.1)</td>
<td>1.1 (1.2)</td>
<td>p=0.912</td>
</tr>
<tr>
<td>At cannulation</td>
<td>2.4 (1.4)</td>
<td>3.4 (1.3)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.3 (1.0)</td>
<td>2.3 (1.2)</td>
<td>p=0.001</td>
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</tbody>
</table>

Differences between treatment groups were analysed using a t-test. The results are consistent across all three groups of pain raters, with the treatment groups being balanced at baseline and clear differences of around one point being evident during cannulation. The differences are similar whether raw scores or change from baseline is considered. The p-values are extreme for the parent and research assistant rating scores. The less extreme values for the child’s own ratings are most likely to be because of the smaller patient numbers, as the point estimates for the difference are very similar.

This trial provides evidence that use of LMX 4 Lidocaine 4% w/w Cream for 30 minutes under occlusion reduces pain during intravenous cannulation.

### SAFETY

Bibliographical evidence and extensive clinical experience make it highly probable that a topical formulation of 4% lidocaine cream will have an acceptable safety
profile. In addition, pharmacokinetic studies have produced no data to suggest a safety concern regarding either systemic absorption or local tolerability.

PRODUCT LITERATURE
All product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) are satisfactory.

CONCLUSION
Granting of a marketing authorisation is acceptable.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of the products are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new Non-clinical data were submitted and none are required for applications of this type.

EFFICACY AND SAFETY

The efficacy of g LMX 4 Lidocaine 4% w/w Cream has been well documented in the past. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.
**LMX 4 LIDOCAINE 4% w/w CREAM**

**PL 20685/0034**

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 19 August 2004</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 6 October 2004</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested information relating to the dossier on 23 February 2006. The applicant responded to the MHRA’s requests, providing further information the dossier on 28 October 2006 and 1 February 2007</td>
</tr>
<tr>
<td>4</td>
<td>The application was considered by the Commission of Human Medicines at a pre-hearing on 15-16 February and a hearing on 15-16 March 2007</td>
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<td>5</td>
<td>Following assessment of the information submitted by the applicant, the MHRA requested information relating to the clinical dossier on 21 August 2007 and the quality dossier on 12 October 2007</td>
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<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information the clinical dossier on 12 October 2007 and the quality dossier on 6 November 2007</td>
</tr>
<tr>
<td>7</td>
<td>A Marketing Authorisation was granted on 20 November 2007</td>
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Module 6

LMX 4 Lidocaine 4% w/w Cream

PL 20685/0034

STEPS TAKEN AFTER ASSESSMENT

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Description</th>
<th>Outcome</th>
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<tr>
<td>31/01/2011</td>
<td>Type II variation</td>
<td>To add a new indication for LMX 4, for use as a topical anaesthetic prior to large surface area dermal treatments in adults and the elderly at a dosage of 1.5 g to 2 g LMX 4 per 10 sqcm skin. Consequentially sections 4.1, 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC leaflet and the label have been updated.</td>
<td>Variation granted 28/06/2013</td>
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ANNEX 1 – CLINICAL VARIATION ASSESSMENT REPORT

Our Reference: PL 20685/0034 - 0023
Product: PL 20685/0034 LMX 4 Lidocaine 4% w/w Cream
Marketing Authorisation Holder: FERNDALE PHARMACEUTICALS LIMITED
Active Ingredient(s): LIDOCAINE.

Reason:
To add a new indication for LMX 4, for use as a topical anaesthetic prior to large surface area dermal treatments in adults and the elderly at a dosage of 1.5 – 2 g LMX 4 per 10 sqcm skin. Consequentially sections 4.1, 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC, leaflet and the label have been updated.

Linked / Related Variation(s) or Case(s):
This is a Type II C.I.6a complex variation application for a new indication for LMX 4: application to large surface areas of intact skin in adults, including the elderly, for the purpose of producing local anaesthesia prior to the execution of painful topical treatments.

LMX 4 is currently approved in the UK for use as a topical local anaesthetic for small areas of skin prior to painful medical procedures such as cannulation or venipuncture. The current approved dosage is 1- 2.5 g cream over a 2.5 cm x 2.5 cm (6.25cm²) area in adults, children over one month of age and the elderly. This Complex C.I.6a Type II variation is to add a new indication for use of LMX 4 as a topical local anaesthetic over larger areas of intact skin, up to 900 cm², at a dosage of 1.5 to 2 g of cream per 10 cm², in adults over 18 years of age, including the elderly. Children and adolescents are excluded.

LMX 4 contains 4% w/w Lidocaine in a liposomal base. The most widely used topical anaesthetic world-wide is a product known as EMLA which contains a mixture of two local anaesthetics – 2.5% w/w lidocaine and 2.5% w/w prilocaine – in an oil-in-water emulsion cream. EMLA is already approved in the UK for use as a topical anaesthetic prior to painful, large surface area dermal procedures. There is therefore a precedent for the use of topical lidocaine over larger areas of skin than are currently approved for LMX 4.

The proposed changes are given in Italics below:

Section 4.1
Add – and for dermal procedures and treatments requiring anaesthesia of large surface areas of skin
Assessor’s comments:
From the submitted information (see assessor’s comments in section 4.2) it is acceptable that larger than currently approved surface areas of skin can be effectively treated with topical lidocaine for a local anaesthetic effect with acceptable safety. However the maximum limit in terms of area of application or in term of dose that is acceptable has not been clearly identified or supported.

Major Clinical point:
- The applicant has not categorically specified the maximum limit in terms of dose and or area of application. This should be specified and the basis for the specification should be supported in terms of the safety, efficacy and pharmacokinetic data of this dose for the recommended maximum duration. This should include the number of patients data available for this dose and duration from published literature and their relevant exposure, efficacy and safety.

Section 4.2
Dermal Procedures and Treatments
‘Adults, including the elderly.
Apply the cream at dosage of approximately 1 g LMX 4/10 cm² skin to be treated, or multiples thereof. Typical estimated larger quantities would be 30 g/300 cm² (approximately 10 cm x 30 cm) or 120 g/1200 cm² (approximately 40 cm x 30 cm). The cream should be applied evenly with a uniform thickness across the area where the dermal procedure or treatment will occur. The cream should remain undisturbed. The LMX 4 Cream should be applied for up to 60 minutes. Prior to starting the procedure, the LMX 4 Cream should be removed using a clean gauze swab and the site for dermal treatment or procedure prepared in the usual manner. The procedure should be initiated approximately 5 minutes after the cream has been removed.’
Not recommended in children for this indication

Supporting evidence:
From EMLA SPC which has 2.5% lidocaine – the dose of 1.5-2 g/10 sq cm is recommended – therefore the dose of LMX 4 which has 4% lidocaine at 1 g/10 sq cm is acceptable from safety point of view.

The duration of application of EMLA for larger surface areas is recommended as minimum of 2 hours and maximum of 5 hours. Here the LMX 4 cream is recommended for application for up to 60 minutes. While this is not a safety issue, whether adequate efficacy will be obtained should be seen from the submitted data. The data the applicant refers to in support is a study in children where LMX 4 and EMLA were compared and it was shown that LMX 4 was faster acting in children. Based on this, it is concluded that LMX 4 applied for 1 hour should be reasonable. In addition, the Qutenza studies (where exact dose applied is not available) used LMX 4 for 60 minutes supports the proposed duration of 60 minutes. This approach is not entirely satisfactory without knowledge of the dose of LMX 4 applied in these studies.
The applicant has not submitted any new clinical data. They have reviewed literature and from other published sources quote 26 clinical studies. Of these around 6 published references from Qutenza dossier has been submitted. Qutenza is a Capsaicin patch and Lidocaine or LMX 4 was applied before application of this patch in clinical development studies of Qutenza. Qutenza is licensed on the basis of these studies and hence these studies can be considered to be of good standard. However the applicant does not have access to these studies per se and have only reviewed/submitted the published information.

To support Pharmacokinetic (PK) information – they have submitted 9 references
To support efficacy – 11 published references
To support safety – 6 published references – some of these in addition support efficacy and the above efficacy and PK studies also support safety.

Evaluation:

From these studies some broad conclusions that can be drawn are:

- Application of topical anaesthetic (including Lidocaine) is effective for larger skin areas
- Application of Lidocaine to larger skin areas for the proposed 1 hour has acceptable safety
- The application of the proposed dose for the proposed duration within the proposed recommendations is unlikely to cause significant systemic exposure that can potentially cause toxicity

However certain other important conclusions remain unsupported and include:
- The applicant has not addressed adequately the basis for the recommended dose (1 g/10 sq cm) and duration (up to 60 minutes) for large areas and why this is considered to be the most appropriate. A discussion supported adequately by evidence for the safety and efficacy of the specified dose and duration in larger areas should be provided

Other clinical points:

- Dermal Procedures and Treatments should be further described with examples; like laser therapy and skin grafting
- Treatment population is not well defined; ‘adults including elderly’ should be defined by age
- The minimum recommended duration of application should be specified and this should be supported
- The minimum dose interval before re-application should be specified and supported

Section 4.4

Do not use in larger quantities than those stated, particularly over raw or blistered areas

Patients receiving cimetidine are at higher risk of developing toxic plasma concentrations of lidocaine since cimetidine inhibits hepatic metabolism by reducing hepatic blood flow.
Patients receiving propranolol are also at higher risk of developing toxic lidocaine levels owing to reduction in lidocaine clearance from plasma.

**Assessor’s comments:**
These statements can be inferred from EMLA SmPC and are established facts. However these are not suitable in Section 4.4 and should be shifted to section 4.5

- The statements on cimetidine and propranolol are drug-interactions, which are appropriate for section 4.5 and not for section 4.4

As one of the basis for this SPC is the SPC of EMLA, the following points which are particularly relevant when Lidocaine is applied to larger areas should be included:

- Advice on close surveillance and consideration of ECG monitoring for cardiac adverse effects when patients on class III anti-arrhythmic drugs (e.g. amiodarone) are treated with topical lidocaine should be included

Patients treated with anti-arrhythmic drugs class III (eg, amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

**Section 4.5**

*Drugs that reduce the clearance of lidocaine (eg cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long period of time. Such interactions should therefore be of no clinical importance following short term treatment with lidocaine (eg LMX 4) at recommended doses.*

The risk of additional systemic toxicity should be considered when large doses of LMX 4 are applied to patients already using other local anaesthetics or structurally related drugs, e.g class I anti-arrhythmics such as mexiletine.

**Assessor’s comments:**
These statements are in EMLA SmPC and are established facts. These are acceptable. However

It is noted that

- The addition of “or structurally related drugs, e.g class I anti-arrhythmics such as mexiletine” is a repetition as this fact is already covered by the first statement in section 4.5 and should therefore be removed
- The potential for methaemoglobinemia in patients who are taking other concomitant drugs as seen in one of the references (SmPC of EMLA) should be included

*This statement from EMLA is not there:*
*Methaemoglobinemia may be accentuated in patients already taking drugs known to induce the condition, e.g. sulphonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, metoclopramide, naphthalene, nitrates and nitrites,*
Conclusion
The use of topical lidocaine for larger areas of skin can have acceptable efficacy and safety as demonstrated in published studies which included studies with LMX 4. However from these studies, a maximum area or dose and the most appropriate dose and duration for larger areas have not been identified or supported. These are major points. In addition, a number of minor points to the proposed textual changes have been raised.

Decision - Request for Further Information

Date: 11th April 2011

Major clinical points:

1) The applicant has not categorically specified the maximum limit in terms of dose and or area of application. This should be specified and the basis for the specification should be supported in terms of the safety, efficacy and pharmacokinetic data of this dose for the recommended maximum duration. This should include the number of patients data available for this dose and duration from published literature and their relevant exposure, efficacy and safety

2) The applicant has not addressed adequately the basis for the recommended dose (1 g/10 sq cm) and duration (up to 60 minutes) for large areas and why this is considered to be the most appropriate. A discussion supported adequately by evidence for the safety and efficacy of the specified dose and duration in larger areas should be provided

Other clinical points:

1) Dermal Procedures and Treatments should be further described with examples; like laser therapy and skin grafting
2) Treatment population is not well defined; ‘adults including elderly’ should be defined by age
3) The minimum recommended duration of application should be specified and this should be supported
4) The minimum dose interval before re-application should be specified and supported
5) The statements on cimetidine and propranolol are drug-interactions, which are appropriate for section 4.5 and not for section 4.4
6) Advice on close surveillance and consideration of ECG monitoring for cardiac adverse effects when patients on class III anti-arrhythmic drugs (e.g. amiodarone) are treated with topical lidocaine should be included
7) The addition of “or structurally related drugs, e.g class I anti-arrhythmics such as mexiletine” is a repetition as this fact is already covered by the first statement in section 4.5 and should therefore be removed
The potential for methaemoglobinaemia in patients who are taking other concomitant drugs as seen in one of the references (SmPC of EMLA) should be included.

The reasons for major clinical point 2 despite their submission of Dose justification discussion document:

A current comparison between SPC of EMLA and LMX 4 shows that dose of LMX 4 is 1 to 2.5g of cream on 6.25 sq cm area for 30 minutes and up to 5 hours, while that of EMLA is 2 g for a minimum of 60 minutes to maximum of 5 hours whereas the current proposed dose and duration for LMX 4 is 50% the maximum dose and 50% of the time duration as compared to EMLA. This proposal is acceptable from a safety perspective but the efficacy is not adequately supported. The other data from Quentaza trials does not appear to have the dose applied information.

Assessment of Response:

In response to the preliminary list of questions raised, the applicant has further reviewed literature and submitted a number of literature references to support the claims. The applicant has used evidences from use of LMX 4, other Lidocaine formulations and of EMLA cream.

The applicant has not provided any bridging for the evidence from other Lidocaine formulations to LMX 4. In the absence of such bridging, these evidences can be considered generally supportive for safety and not for making any specific claims on indications or dosage recommendations.

For the evidence from EMLA cream, there are two studies which can be considered to be bridging to the LMX 4 formulation. However the applicant has not thoroughly discussed this aspect. One study compared EMLA and LMX 4 prior to venous cannulation. However as there is a potential for difference in efficacy and safety for the indications where application of the topical treatments to a larger skin surface area is involved, this study is not considered adequate to support claims beyond that specific indication. The second study is comparison of EMLA and LMX 4 in the Qutenza package. The study data is not available and it is not possible to conclude if the LMX 4 and EMLA were just comparable or similar. Hence in the absence of robust bridging data, the inferences on indications and dosages from EMLA cannot be ascribed to LMX 4.

In addition, the proposed variation has been extended in scope as below:

a) While the initial variation was for an indication in adults, now the proposal is to include children also for the claimed indication of treating large skin surface areas

b) Further the indications have been specifically named now to include laser procedures, multiple needle insertions, chemical peeling and the application of topical treatments that can cause dermal pain.
The applicant was given guidance on the data requirements to support these claim. Some of the recommendations that were made for the applicant’s consideration include:

- Area of use – 1000 sq cm
- Duration of use – Some studies have shown that onset of action may be as early as 30 minutes. However as most of the well collected data used 60 minutes, this duration is recommended. There is data to suggest that durations of application up to 5 hours has acceptable safety profile. So in case adequate clinical response is not achieved longer durations up to 5 hours may be used.
- Indications – Larger surface area like relieving pain before application of topical treatments that may cause pain like quetenza

The following may be the best output which will however be reviewed based on the applicant’s response.

a) for use on larger surface areas of skin before application of painful topical patches, where indicated
b) wash off the lidocaine before application of the topical patches

Enclosed below is the assessment of response to the specific questions, assessment of supporting evidence and the list of questions in the RFI.

**Assessment of response to questions:**

**Major clinical points:**

1) The applicant has not categorically specified the maximum limit in terms of dose and area of application. This should be specified and the basis for the specification should be supported in terms of the safety, efficacy and pharmacokinetic data of this dose for the recommended maximum duration. This should include the number of patients data available for this dose and duration from published literature and their relevant exposure, efficacy and safety.

The applicant has now specified the maximum limit in terms of dose and area of application. The area remains at 1200 sq cm but the dose has increase by 50% from 1 g/sq cm to 1-1.5 g/sq cm. Further the applicant has now proposed inclusion of paediatric population for this indication from age 1 month onwards.

The basis for the above proposal is based on PK data and extrapolation to safety from systemic lidocaine use. EMLA is approved at 1.5 -2 g/10 sq cm (this based on PK is equal to 1-1.4 g/10 sq cm of LMX 4) – so applicant claims 1-1.5 g/10 sq cm. Literature of EMLA, other lidocaine formulations and LMX 4 where available, have all been discussed without discussing the weight of each different evidence in terms of supporting the proposals or claims.

The issue is not resolved.

The proposed maximum limit in terms of dose and area of application is based on extrapolations and assumptions which are not considered adequately supportive. The application should re-evaluate the clinical data and base these on actual clinical data available.

2) The applicant has not addressed adequately the basis for the recommended dose (1 g/10 sq cm) and duration (up to 60 minutes) for large areas and why this is considered to be the most appropriate. A discussion
The applicant has now specified the maximum limit in terms of dose and area of application. The area remains at 1200 sq cm but the dose has increase by 50% from 1 g/sq cm to 1-1.5 g/sq cm. Further the applicant has now proposed inclusion of paediatric population for this indication from age 1 month onwards

The basis for the above proposal is based on PK data and extrapolation to safety from systemic lidocaine use. Literature of EMLA, other lidocaine formulations and LMX-4 where available, have all been discussed without discussing the weight of each different evidence in terms of supporting the proposals or claims.

Safety – is apparently based on lower systemic levels than the known toxic systemic levels (expressed as 5 mcg/l – which is the toxic levels of lidocaine reported for systemic use)

Efficacy – based on the lowest concentration used for the shortest time 1 g/10 sq cm for 30 minutes has been shown to be efficacious. Further, the duration of application ranges from 30 minutes to 5 hours which is considered sufficient. So currently a range for the dose 1 -1.5 g and a range for the duration 30 minutes to 5 hours are proposed.

   a) 30 minutes as minimum duration of application for onset of action is acceptable based on comparative clinical study
   b) 5 hours as maximum duration of application based on safety of lidocaine applied for nearly 24 hours and
   c) Total systemic exposure is likely to be below the systemic toxic levels of 5 mcg/ml

The issue is not resolved.

The proposed dose range and range of duration is based on toxic levels of lidocaine (5 mcg/ml) reported for systemic use of lidocaine. For topical use, a concentration (1 mcg/ml) sufficient to cause systemic pharmacological activity may be considered undesirable and hence this is the appropriate concentration to base the dose range. The applicant is therefore required to re-evaluate the data and propose the dose range and range of duration. When a dose range and duration range is being suggested, it is also better to propose a definitive recommendation on the dose and/or duration for which clinical data with LMX 4 is available.

Other clinical points:

   1) Dermal Procedures and Treatments should be further described with examples; like laser therapy and skin grafting

This has been done. However the evidence for each should be clearly explained whether this is supported by data from LMX 4 or is transposed from other products like EMLA. Lidocaine etc. If it is the latter then the strength of association between LMX 4 and this data should be clearly explained. This is now a major point as some of the proposed indications are not adequately supported.

Point partially resolved.

The applicant should provide supporting data for each of the proposed indications like laser procedures, multiple needle insertions, chemical peeling and the application of topical treatments that can cause dermal pain. Only the examples for which sufficient evidence is available should be proposed.

   2) Treatment population is not well defined; ‘adults including elderly’ should be defined by age

The applicant has now proposed all ages from 1 month onwards. The data for supporting each age group is not clearly explained. See major objection 1.

Point not resolved.
There is no clinical data available for use of LMX 4 in large surface areas and in addition appropriate bridging to EMLA data has not been provided. Therefore the proposal to include children is not adequately supported.

3) The minimum recommended duration of application of LMX 4 should be specified and this should be supported

The minimum duration recommended is 30 minutes and this is based on literature from other Lidocaine formulations. The applicability of those results to the LMX 4 formulation is not explained.

Point partially resolved.
See comment for point 2

4) The minimum dose interval before re-application should be specified and supported

A minimum dose interval of 12 hours is proposed. This is supported by the pharmacokinetic data

Point resolved.

5) The statements on cimetidine and propranolol are drug-interactions, which are appropriate for section 4.5 and not for section 4.4 as proposed

Revised SmPC fragments have been provided.

Point resolved.

6) Advice on close surveillance and consideration of ECG monitoring for cardiac adverse effects when patients on class III anti-arrhythmic drugs (e.g. amiodarone) are treated with topical lidocaine should be included in section 4.4

Revised SmPC fragments have been provided.

Point resolved.

7) The addition of “or structurally related drugs, e.g class I anti-arrhythmics such as mexiletine” is a repetition as this fact is already covered by the first statement in section 4.5 and should therefore be removed

Revised SmPC fragments have been provided.

Point resolved.

8) The potential for methaemoglobinaemia in patients who are taking other concomitant drugs as seen in one of the references (SmPC of EMLA) should be included in section 4.5

The applicant has explained that the potential for methaemoglobinaemias is due to the prilocaine in EMLA and therefore this warning is not relevant to a Lidoacine alone preparation.

Point Resolved.

Assessment of supporting evidence:
The supporting evidence is described under pharmacokinetics, efficacy and safety:
Pharmacokinetics:

A. Summaries of Human Pharmacokinetic Studies of LMX4 and similar lidocaine formulations.

<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>Quinzena FDA Drug Approval Package (refs 20, 24-26, 32-34)</td>
<td>Patients treated with layer of LMX4 for 60 minutes on areas up to 1200cm² prior to Capsaicin patch application. Serum lidocaine levels measured after LMX4 removal and prior to Capsaicin patch application in several studies.</td>
<td>Adults with Postherpetic Neuralgia (PHN) or HIV-associated distal symmetrical polyneuropathy (HIV-AN)</td>
<td>2357 subjects across all studies. Specific data available for: Study C109 - 39 adults (Sex not specified);</td>
<td>Not specified</td>
<td>Lidocaine levels 0.57-494ng/ml. Majority of levels &lt; 50ng/ml, max level of 494ng/ml detected with 948cm² Quinzena application area (1080cm² LMX4)</td>
</tr>
<tr>
<td>Seiberling and Keller (ref 4) Study EMD 37740/H101/SPC 317-8</td>
<td>24 Healthy subjects received a single treatment of 5g EMLA (reference) and three treatments of 5g LMX4 (test) over 3 consecutive days (test reference treatments separated by 7 days) on 50cm² area of the arm.</td>
<td>Healthy adults</td>
<td>24 (5 female, 19 male)</td>
<td>18-65 years of age</td>
<td>Lidocaine levels detectable in 10 of 27 patients. Majority of levels &lt; 50ng/ml. Max level of 90.8ng/ml detected with 600cm² Quinzena application area (1600cm² LMX4).</td>
</tr>
<tr>
<td>Stoltz R (2001) (ref 10)</td>
<td>3g LMX4 or EMLA/5.25cm² for 30 minutes</td>
<td>Children</td>
<td>12</td>
<td>2-5y</td>
<td>Mean maximum lidocaine serum level 1 dose of LMX4 was 13.88ng/ml. Mean max level after 3 treatments was 31.58ng/ml. Highest recorded lidocaine plasma level was 172ng/ml.</td>
</tr>
</tbody>
</table>

There are only 3 studies where LMX 4 has been evaluated, of which PK study by Seiberling and Keller – the most reliable.

This study compared PK of EMLA and LMX 4. Dose 5 g on 50 sq cm area. C_max was 172 ng/ml. The exposure of lidocaine from LMX 4 is higher than that of EMLA, however this is explained by the difference in concentration at administration. On 3 consecutive days of administration, the C_max on day 3 and AUC were increased, suggesting significant accumulation.

PK study (Stoltz R 2001)

3 g LMX 4 or EMLA on 6.25 sq cm in 12 children aged 2-5 years – The results show that EMLA was relatively more absorbed – plasma samples only till 4 hours were taken and so is not conclusive

In 2002, Stoltz carried out another PK study where:
3 g LMX 4/25 sq cm 5% Lidocaine on 25 sq cm in 15 children aged 12-18 years – This is not 4% product and results are not useful for this application.

Some PK data in healthy adults and limited PK data in 2-5 year old children are available. The reassurance on systemic safety is acceptable only in adults.

1. The PK data of LMX 4 is compared with PK of EMLA in one study in adults and one study in 2-5 year old. Study in adults showed that exposure of LMX 4
was higher than EMLA (however it is not clear if the exposure was corrected for the administered dose), while PK study in children showed when adjusted for concentrations exposure of lidocaine from EMLA was higher. The applicant should clarify. Further when basing any proposals of dose, duration or area of application using PK data it must be remembered that extrapolation to larger doses, larger areas and different populations beyond the range of actual data is not acceptable.

PK is not adequately characterised and may not be required considering the PK data available for systemic lidocaine use in literature. The PK data is being used only to provide reassurance regarding systemic safety. PK data is available only on healthy skin. PK data in comparison to EMLA is not interpretable.

**Efficacy**

**B. Summaries of efficacy and safety studies of LMX4 and similar lidocaine formulations**

<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>RA Guardiano and CW Nowood [ref 41] USA</td>
<td>Adult volunteers 64 Age not specified 40 male, 24 female</td>
<td>Randomised comparative efficacy study. Degree of anaesthesia produced for Nd:YAG 1,064 laser hair removal.</td>
<td>5g EMLA or LMX4 applied without occlusion for 30minutes (estimated 125cm² area). Pain during laser hair removal assessed using 100mm VAS scale.</td>
<td>Both creams were equally effective for providing pain relief for laser hair removal after 30 minute treatment. No significant difference between male and female subjects.</td>
</tr>
<tr>
<td>EL Carter CA Coppola, FA Barsanti [ref 37] USA</td>
<td>Adults with hyperpigmented papules on the face and/or neck 40 Age range 24-63 years, mean 41 years. 57 female, 3 male</td>
<td>Randomised comparative efficacy study. Degree of anaesthesia produced for electrodesiccation of papules of dermatosis papulosa nigra</td>
<td>6.5g EMLA or LMX4 applied in a 1 to 2mm thick layer with occlusion. Pain during electrodesiccation was assessed using an 11-point numeric scale.</td>
<td>Both creams provided equally effective analgesia for the electrodesiccation process. Safety: One subject treated with each cream experienced burning or stinging. No significant differences in the proportions of adverse events experienced using either cream.</td>
</tr>
<tr>
<td>RA Koppel KM Coleman, WP Coleman [ref 38] USA</td>
<td>Patients undergoing facial peels 10 Age not specified Mean age 35y Gender 5F, 7M</td>
<td>Comparative placebo controlled study. Degree and duration of anaesthesia produced. Faces coated with 7% 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>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Design</td>
<td>Intervention/Outcome</td>
<td>Results</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Quenterza Study C111 [ref 20] USA</td>
<td>Adults with PDN, HIV-AN or PHN</td>
<td>Randomised, open label study of the tolerability of 3 local anaesthetic formulations in conjunction with Quenterza for the treatment of PHN.</td>
<td>Specified area coated with a layer of specified cream (Beticaine, LMX4 or topicaine) for 60 minutes prior to treatment with Capsacin patch.</td>
<td>All three topical anaesthetics gave adequate anaesthesia for application of the Quenterza patch.</td>
</tr>
<tr>
<td>Friedman, JF, Goldstein, K, Nour, VJ, Levine, RB, Ashinoff [ref 3] USA</td>
<td>Adult volunteers 18-75 years of age</td>
<td>Comparative placebo controlled study</td>
<td>Equal amounts of EMLA, LMX4, 4% tetracaine cream, betaine-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 betaine-LA and tetracaine. EMLA was significantly better than betaine-LA. Mean pain scores for all 4 agents after 30 mins were lower, but not significantly. Safety occasional transient local blanching and erythema reported.</td>
</tr>
<tr>
<td>Quenterza studies C116 &amp; C117 [ref 20] USA</td>
<td></td>
<td>Randomise double blind controlled studies with Quenterza for treatment of PHN. LMX4 degree of anaesthesia as pre-treatment for Quenterza patch.</td>
<td>LMX4 applied to specified area up to 12x10cm² prior to Quenterza or control patch application. Adverse events relating to the control patch (3ug/cm² capsaicin compared with 640ug/cm² Quenterza patch) may be attributed to LMX4 pre-treatment.</td>
<td>Pooled analysis of C116 and C117 safety data showed 351 of 401 control group participants experienced at least one adverse event during the study. Over 75% of these were application site reactions including erythema and pain. All adverse reactions were transient and resolved within 1 to 3 days. Patients with BP, HR showed no significant deviations from normal in the Quenterza and control groups. Only 2/43 control group patients experienced BP-related adverse events on the day of treatment. Concluded that LMX4 did not cause significant adverse events during these studies.</td>
</tr>
<tr>
<td>Sieberting and Keller [ref 6]</td>
<td>Adult volunteers 24 18-55 years of age 55/18M</td>
<td>Repeat use clinical safety study. Assessment of adverse events, patients vital and serum lidocaine levels.</td>
<td>24 subjects received a single treatment of 5g EMLA (reference) and three treatments of 5g LMX4 (test) over 3 consecutive days (test reference treatments separated by 7 days) on 5cm² area of the arm. LMX4 not removed from skin between the 3 applications.</td>
<td>No serious or severe adverse events reported for either LMX4 or EMLA. The two moderate (both LMX4) and six mild (3 LMX4, 3 EMLA) adverse events reported after the specified treatment treatment were considered unlikely related to the study drug. Patients vital (BP, HR and body temperature) over the 72 hour LMX4 treatment range showed no clinically relevant deviations from the normal range. One patient had an abnormal ECG at the end of the study, judged as not clinically significant.</td>
</tr>
<tr>
<td>Rowbotham 1995 [ref 17]</td>
<td>Adults with PHN 30 subjects</td>
<td>Efficacy &amp; safety study</td>
<td>Patients treated with 5% lidocaine gel or vehicle gel applied to area of PHN pain for 24 hours (limb or torso) or 8 hours (cranium)</td>
<td>No systemic adverse effects seen after gel application at any time point.</td>
</tr>
<tr>
<td>Nestor [ref 13]</td>
<td>Healthy adults 21-75y 8 subjects</td>
<td>Safety study</td>
<td>Patients treated with 30g or 50g LMX4 with occlusion at 10g/100cm² to 300cm² or 600cm²</td>
<td>No neurological side effects of lidocaine observed. No cardiovascular effects of lidocaine observed.</td>
</tr>
<tr>
<td>Quenterza study C118 [ref 22]</td>
<td>Adults with PHN 18-90y 108 subjects</td>
<td>Safety study</td>
<td>LMX4 applied for 60 minutes to skin areas up to 12x10cm² prior to capsacin patch application.</td>
<td>Only transient changes in BP, HR, and RR reported following topical anaesthetic application.</td>
</tr>
</tbody>
</table>
Substantial clinical data of use of LMX 4 is available from the Qutenza package. The complete details of the use and benefits of LMX 4 is not readily discernable from the available literature. Despite these constraints it is seen from the approved SmPC of Qutenza that a topical local anaesthetic should be applied prior to application of the Qutenza patches. This confirms the benefits of the topical local anaesthetic patch for this indication. There are strong indications to suggest that the topical anaesthetic used was LMX 4, however this needs to be further confirmed. A couple of clarification points have been raised in this regard.

The applicant has provided a number of literature evidences from other topical lidocaine formulations and EMLA cream to support the proposed indications. However, as discussed before adequate bridging of LMX 4 to this data has not been provided. It is noted that there is some data on use of LMX 4 in indications like laser hair removal, electrodesiccation of papules and facial peels. As presented this data does not appear to be supportive for claiming these indications. The applicant needs to re-evaluate these data and discuss if the data is conclusive of the efficacy of LMX 4 when supported with additional justifications, additional data from literature specific to these indications and/or bridging.

Safety

There is literature from Qutenza studies to support the safety of the use of topical lidocaine in large surface areas of skin. Further data from EMLA cream is also supportive of the use of topical lidocaine in large surface areas of skin. There is also literature to show that higher concentrations of other topical lidocaine formulations and for longer durations of use than proposed have had acceptable safety profile. Further there is data to show repeated administrations of topical lidocaine is also well tolerated.

In addition, there is a lot of evidence on the systemic use of lidocaine with acceptable safety profile, which provides reassurance on the safety. As long as the worst case estimates of the systemic exposure after topical application of LMX 4 is seen to be below the pharmacological active systemic levels, the safety profile for the use of topical LMX 4 in larger intact skin areas can be considered acceptable.

Request for Information (RFI):

Major Points:

1. The proposed maximum limit in terms of dose and area of application is based on extrapolations and assumptions which are not considered adequately supportive. The application should re-evaluate the clinical data and base these on actual clinical data available.

2. The proposed dose range and range of duration is based on toxic levels of lidocaine reported for systemic use of lidocaine. For topical use, a systemic concentration sufficient to cause systemic pharmacological activity may be considered undesirable and hence this is the appropriate concentration to base the dose range. The applicant is therefore required to re-evaluate the data and propose the dose range and range of duration accordingly. Further, when a dose range and duration range is being suggested, it is also better to propose a definitive recommendation on the dose and/or duration for which clinical data with LMX-4 is available.
3. The applicant should provide supporting data for each of the proposed indication like laser procedures, multiple needle insertions, chemical peeling and the application of topical treatments that can cause dermal pain. Only the examples for which sufficient evidence is available should be proposed.

4. There is no clinical data available for use of LMX-4 in large surface areas in children and in addition appropriate bridging to EMLA data has not been provided. Therefore the proposal to include children is not adequately supported.

Other Concerns:

1. The PK data of LMX-4 in comparison to EMLA from the two studies should be clarified further after adjusting for administered dose of Lidocaine to determine conclusively which of the formulations have a higher systemic bioavailability.

2. When basing any proposals of dose, duration or area of application using PK data it must be remembered that extrapolation to larger doses, larger areas and different populations beyond the range of actual data is not acceptable.

3. The applicant should provide a statement /Literature to confirm that the studies of qutenza used the medicinal product LMX-4. Further the applicant should provide assurance that the product LMX-4 and other names referred for LMX-4 in the literatures from different geographic regions are the same product.

4. In the absence of placebo-comparator data, the efficacy of lidocaine in reduction of pain due to administration of topical treatments like Qutenza should be further discussed. Further in the absence of actual doses of LMX-4 used in the Qutenza studies, the proposed doses should be justified appropriately.

5. The applicant has provided a number of literature evidences of LMX-4, other topical lidocaine formulations and EMLA cream to support the proposed indications. However adequate bridging of LMX-4 to the data from EMLA and other topical lidocaine formulations has not been provided. It is noted that there is some data on use of LMX-4 in indications like laser hair removal, electrodesiccation of papules and facial peels. As presented this data does not appear to be supportive for claiming these indications. The applicant needs to re-evaluate these data and discuss if the data is conclusive of the efficacy of LMX-4 when supported with additional justifications, additional data from literature specific to these indications and/or bridging.

Final Assessment 27th June 2013

Assessor overall evaluation: This Type II complex variation application does not contain any new clinical data but presents a range of published evidence from the literature relating to clinical studies using a variety of lidocaine formulations, including LMX 4 and EMLA, in a variety of contexts including large surface area application prior to the execution of painful topical procedures. From this evidence, collectively, it is reasonable to conclude that there will be an acceptable level of safety and efficacy when LMX 4 is used topically at a dose of 1.5-2 g of cream per 10 cm² of skin for the induction of local anaesthesia over an area of skin up to a maximum of 900 cm², prior to the execution of painful procedures. This indication is restricted to the adult population over 18 years of age, including the elderly, and is only for use on intact skin and not mucous membranes.
A principal concern regarding the large surface area application of LMX 4 relates to the potential for systemic lidocaine toxicity following trans-cutaneous absorption of the drug, as this new indication represents an increase in dose of more than two orders of magnitude (>100x) above the currently recommended LMX 4 dose for small surface area application. Particular attention has therefore been paid in the assessment to safety. Overt systemic toxicity (manifesting as neurological and cardiac disturbance in particular) can occur at plasma lidocaine levels of 5 µg/ml and above; systemic effects, though not frank toxicity, can be observed at levels of 1 µg/ml. Topical treatment should therefore be associated with plasma levels below the lowest systemic effect level and preferably substantially below this.

Systemic absorption of lidocaine is low but not negligible following topical application to intact skin. Absorption is increased however when the integrity of the cutaneous barrier is disrupted as in wounded or ulcerated skin; furthermore, absorption is increased from mucous membranes. The applicants are therefore correctly cautious in restricting use to intact skin.

**Major Point:**

1) The proposed maximum limit in terms of dose and area of application is based on extrapolations and assumptions which are not considered adequately supportive. The application should re-evaluate the clinical data and base these on actual clinical data available.

The applicants initially proposed a maximum dose of LMX 4 of 1 g/10cm² up to a maximum area of skin of 1200 cm². This has now been modified to a dose of 1.5 to 2 g/10 cm² up to a maximum area of 900 cm²; this is to bring it in line with the approved dose of EMLA for application to large surface areas of skin. This is justified on the following grounds. LMX 4 contains 4% w/w lidocaine whereas EMLA contains 2.5% lidocaine w/w. Thus, the [lidocaine] concentration in EMLA cream is 0.6 times that in LMX 4. Importantly however this is offset by an increased bioavailability of lidocaine from EMLA compared to LMX 4 owing to their different formulations. Three studies in particular compared the bioavailability of lidocaine from EMLA and LMX 4: Sieberling and Keller (2006), Stolz (2001) and Oni (2012) all of which showed higher bioavailability of lidocaine from EMLA compared to LMX 4. As reported in these studies, the ratio of lidocaine bioavailability for LMX 4:EMLA was 0.5-0.8:1. Thus, the higher percentage of lidocaine in LMX 4 compared to that in EMLA is sufficiently offset by its lower bioavailability to allow a recommended dose of cream that is the same as that approved for EMLA. It is therefore justified on safety grounds to bring the dose range for the two products in line with each other and will lessen the risk of clinician application error.

Further justification for the safety of LMX 4 when applied at the same dose as EMLA over a large surface area of skin can be reasonably inferred from an extensive clinical study that compared treatment with EMLA versus LMX 4 prior to the application of up to 4 capsaicin patches (marketed as Qutenza), a symptomatic treatment for peripheral neuropathy that is itself acutely painful upon initial application. LMX 4 was applied to areas of skin up to a maximum of 1200 cm² in comparable amounts to those administered in the EMLA treatment arm. The data formed part of an FDA Drug Approval package and although the LMX 4 dose was not explicitly stated, a
subsequent publication clarified the EMLA dosage to be 1-2 g/10 cm² and therefore it can be reasonably inferred that LMX 4 was applied in the same amounts. In these studies the majority of the systemic lidocaine levels were below the limit of quantitation (50 ng/ml); however, among subjects who received the largest dose of LMX 4, plasma levels were higher but the highest levels were recorded as ~0.5 µg/ml which is 10% of the level at which overt toxicity occurs and 50% of the systemic effect level.

The study by Oni (2012) also supports the safety of LMX 4 when applied to large areas. In this study 30 g of LMX 4 was applied to the face over an area of 300 cm² for 60 minutes, with occlusion (which is known to enhance the absorption of local anaesthetics). Even under these conditions, C_max was in the region of 0.5 µg/ml which is still substantially below a toxic plasma level.

Supportive data are also provided by a study using EMLA in which a “thick” layer of cream (providing a dose of 1.5-3 g/10 cm²) was applied to large areas of skin >1000 cm² during skin grafting. Maximum plasma levels of lidocaine were in the region of 0.5 µg/ml which is 50% of systemic effect levels.

Assessor evaluation: this point has been resolved.

**Major point:**

2) The proposed dose range and range of duration is based on toxic levels of lidocaine reported for systemic use of lidocaine. For topical use, a systemic concentration sufficient to cause systemic pharmacological activity may be considered undesirable and hence this is the appropriate concentration to base the dose range. The applicant is therefore required to re-evaluate the data and propose the dose range and range of duration accordingly. Further, when a dose range and duration range is being suggested, it is also better to propose a definitive recommendation on the dose and/or duration for which clinical data with LMX-4 is available.

The new indication for application of LMX 4 to large areas of skin is intended for the acute induction of local anaesthesia prior to the execution of painful procedures and it is not intended for the management of chronic painful conditions. Application times of 30 to 60 minutes, or until adequate analgesia is achieved, are proposed.

Efficacy and safety of LMX 4 with application times of 30-60 minutes are adequately shown by the Qutenza data. Longer application times (24 hours) to smaller areas (Sieberling and Keller) caused no serious local adverse effects. Safety of longer application times is also supported by use of EMLA in skin grafting studies in which EMLA was applied for up to 5 hours to large areas.

Although single application is likely to be the more frequent mode of administration, one or more repeat applications of LMX 4 may be required to cover the acute period. It is important therefore to consider the minimum interval between applications of LMX 4 in order to avoid cumulative toxicity. The applicants present evidence from the literature that trans-cutaneous absorption of LMX 4 proceeds slowly and that the time taken to reach C_max within plasma, T_max, is of the order of 11.6 hours. The Sieberling and Keller study, in which topical LMX 4 and EMLA were applied once daily, without removal, for three consecutive days, disclosed that the plasma...
elimination half-life of lidocaine following topical application of LMX 4 is ~24 h and that for topically applied EMLA of ~62 hours; this compares with a plasma elimination half-life following an IV bolus of lidocaine of the order of 1-1.5 hours in adults although this extends to 2.5 hours in elderly patients. The Sieberling and Keller study highlights the risk of plasma accumulation when cream is not removed following induction of anaesthesia as this greatly extends the plasma half-life. The current application therefore recommends removal of LMX 4 once anaesthesia is achieved and a minimum interval of 12 hours between applications of LMX 4 is recommended. This dosing interval would be anticipated to produce some accumulation within plasma but given the margin of safety in the C_{max} after single application to large areas, this is unlikely to reach hazardous levels, particularly if the cream is removed once anaesthesia is achieved which is what is recommended. Reassurance is also provided by a published study into repeated application of 5% lidocaine patches to the skin of healthy volunteers for periods of 12 hours with 12 hour rest periods in between. No significant systemic accumulation of lidocaine was observed in this study. Furthermore, the SPC for the new indication for LMX 4 warns of the potential danger of systemic accumulation with repeated administration.

Assessor evaluation: this point has been resolved

Major point:

3) The applicant should provide supporting data for each of the proposed indication like laser procedures, multiple needle insertions, chemical peeling and the application of topical treatments that can cause dermal pain. Only the examples for which sufficient evidence is available should be proposed.

In light of a range of supporting data for a variety of painful dermal procedures, the applicant now propose the indication as follows: “prior to administration of painful topical treatments on larger surface areas of intact skin”, instead of listing individual treatments. Evidence from the literature that specifically refers to LMX 4 is now provided. Cited clinical studies include: Qutenza (capsaicin patch) studies showed comparable efficacy between LMX 4 and EMLA; Altman and Gildenberg (1999) showed comparable efficacy between LMX 4 and EMLA prior to laser hair removal; Koppel demonstrated comparable efficacy between EMLA and LMX 4 for chemical skin peels; Carter showed comparable efficacy between LMX 4 and EMLA prior to electrodessication of facial papules; Herberger (2011) showed comparable efficacy between EMLA and LMX 4 prior to multiple pinpricks (to mimic a variety of minor surgical procedures). Thus, the efficacy of LMX 4 has been adequately demonstrated for a range of painful procedures and therefore it is justified to use the generic term “painful topical treatments” when defining the treatment context.

Assessor evaluation: this point has been resolved

Major point:

4) There is no clinical data available for use of LMX 4 in large surface areas in children and in addition appropriate bridging to EMLA data has not been provided. Therefore the proposal to include children is not adequately supported.

The applicants have removed the indication for children and will only be available for adults over 18 years of age, including the elderly. Elderly patients would be expected
to be more susceptible to lidocaine toxicity due to its slower elimination in this age group and the presence of cardiovascular and other co-morbidity, coupled with thinner and therefore more permeable skin. A number of the published safety and efficacy studies using topical lidocaine incorporated geriatric patients, in particular Qutenza studies using LMX 4 which included patients up to age of 82 years. Several of the EMLA studies included geriatric patients up to 90 years of age and older. LMX 4 is therefore justified for use in elderly patients with the cautions and provisos already stated.

Assessor evaluation: this point has been resolved

Other point:

1) The PK data of LMX-4 in comparison to EMLA from the two studies should be clarified further after adjusting for administered dose of Lidocaine to determine conclusively which of the formulations have a higher systemic bioavailability.

As discussed under Major Point 1, the [lidocaine] in EMLA is 0.6 times that in LMX 4 however this is offset by a lower systemic bioavailability of lidocaine when present in LMX 4 (0.5-0.8 compared to that in EMLA), as evidenced in the studies cited above. Thus, the amount of lidocaine that is delivered systemically can be reasonably deduced to be comparable for LMX 4 and EMLA per g of cream.

Assessor evaluation: this point has been resolved

Other point:

2) When basing any proposals of dose, duration or area of application using PK data it must be remembered that extrapolation to larger doses, larger areas and different populations beyond the range of actual data is not acceptable.

As discussed under Major Point 1, proposed dose, duration and area of application for LMX 4 is now evidenced by PK data using LMX 4 and not by extrapolation.

Assessor evaluation: this point has been resolved

Other point:

3) The applicant should provide a statement /Literature to confirm that the studies of qutenza used the medicinal product LMX-4. Further the applicant should provide assurance that the product LMX-4 and other names referred for LMX-4 in the literatures from different geographic regions are the same product.

A signed statement to confirm that the Qutenza studies used LMX 4 is provided and other references cite the supplier of LMX 4 or ELA-Max as Ferndale Inc, confirming its identity as LMX 4.

Assessor evaluation: this point has been resolved

Other point:
4) In the absence of placebo-comparator data, the efficacy of lidocaine in reduction of pain due to administration of topical treatments like Qutenza should be further discussed. Further in the absence of actual doses of LMX-4 used in the Qutenza studies, the proposed doses should be justified appropriately.

The FDA Drug Approval package for Qutenza (capsaicin patch) contained extensive clinical studies that included comparative analysis of the efficacy of LMX 4 and EMLA when applied topically for 60 minutes prior to the application of up to 4 capsaicin patches. Pain was rated on a visual analogue scale and LMX 4 and EMLA were found to be therapeutically equivalent in terms of overall anaesthetic effect.

As outlined above under Major point 1, the dose of lidocaine per unit quantity of LMX 4 and EMLA cream that is absorbed systemically is essentially equivalent when relative concentration of lidocaine between the two products and their different bioavailability are taken into account. However, this is only relevant to safety of the product and not to its efficacy as a local anaesthetic. Lidocaine is present at a higher concentration (4% w/w) in LMX 4 cream compared to 2.5% lidocaine in EMLA; EMLA also contains a second local anaesthetic, prilocaine, at 2.5%, the two agents acting additively though not synergistically to produce an anaesthetic effect. It is important therefore to determine whether LMX 4 is equivalent to EMLA in terms of its therapeutic effect as EMLA is the gold standard topical anaesthetic that is used world-wide.

As discussed above, it is reasonable to conclude both from the FDA package and from a published report of the trial that the same amounts of LMX 4 and EMLA cream were used in the Qutenza trials. Therefore, LMX 4 treatment would have been associated with a 1.6 times higher quantity of lidocaine being applied to the area of skin than with EMLA; however, EMLA also contains prilocaine which will assist in its local anaesthetic action. The comparative efficacy analysis revealed that LMX 4 and EMLA were equivalent in terms of anaesthetic action from which it can be concluded that the combined presence of prilocaine with lidocaine at 2.5% w/w for each does not offer superior anaesthetic action for this application compared to lidocaine alone at 4% w/w.

Therapeutic equivalence between EMLA and LMX 4 is further supported by the range of studies discussed under Major Point 3.

Assessor evaluation: this point has been resolved

Other point:

5) The applicant has provided a number of literature evidences of LMX-4, other topical lidocaine formulations and EMLA cream to support the proposed indications. However adequate bridging of LMX-4 to the data from EMLA and other topical lidocaine formulations has not been provided. It is noted that there is some data on use of LMX-4 in indications like laser hair removal, electrodesiccation of papules and facial peels. As presented this data does not appear to be supportive for claiming these indications. The applicant needs to re-evaluate these data and discuss if the data is conclusive of the efficacy of LMX-4 when supported with additional justifications, additional data from literature specific to these indications and/or bridging.
This point is addressed under Major Point 3.

Assessor evaluation: this point has been resolved

Assessor comment: The wording in section 5.2 of SmPC, final paragraph relates specifically to persistence of anaesthesia following removal of cream which is not central to the new indication has been removed. Furthermore, the supplied references do not adequately support this in large dermal area application. The preceding paragraph (commencing LMX4 has been shown to provide…..) should be moved to section 5.1 of the SmPC as it relates to pharmacodynamic properties. Amended 5.1 and 5.2 fragments now provided and are acceptable.

Final Assessor comment on SPC, leaflet and label: the amendments to the SPC, patient information leaflet and package label are all in line with implementation of the new indication in a safe and appropriate manner. The amendments to sections 5.1 and 5.2 of the SPC are also acceptable.

Concluding assessment: all outstanding issues have been resolved and the application can proceed to approval.
Summary of Product Characteristics

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

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Label:

L.M.X.4
lidocaine 4% w/w cream

Active Ingredient:
1g cream contains 40mg lidocaine.

Also contains: Benzyl alcohol, carbomer, cholesterol, phospholidip 80H, polysorbate 80, propylene glyco, tiodamine, vitamin E acetate and purified water.

Exempt with well-known effect, propylene glycol which may cause skin irritation.

5g e

For use as a local anaesthetic to produce numbness of the skin for temporary relief of pain associated with venous cannulation and venipuncture.

Directions: For cutaneous use: Read enclosed leaflet before use or use as directed by a medical practitioner.

FOR EXTERNAL USE ONLY
Do not store above 25°C
Keep out of the sight & reach of children

Marketing Authorisation holder

FERNDALE
Pharmaceuticals

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