SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LMX 4

Lidocaine 4%w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lidocaine 4%w/w

Excipient with known effect:
1 gram of cream contains 75mg of propylene glycol.
1 gram of cream contains 15mg of benzyl alcohol.
1 gram of cream contains 7.5mg of polysorbate 80.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Cream

A white to off-white yellowish cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Local anaesthetic for topical use to produce surface anaesthesia of the skin prior to:

- venous cannulation or venipuncture
- administration of painful topical treatments on larger surface areas of intact skin where use of a topical anaesthetic is appropriate.

4.2 Posology and method of administration

For cutaneous use only.

Venous cannulation or venipuncture:

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 5g tube, or 3.5cm from the 30g 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, but the LMX4 Cream may be applied for up to 5 hours under a dressing. Prior to starting the procedure, the LMX4 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 shortly after the cream has been removed. Maximum application time for 1 month up to 3 month infant should not exceed 60 minutes. Maximum application time for 3 month up to 12 month infant should not exceed 4 hours. Maximum application for 12 month infant – adult should not exceed 5 hours.

LMX4 is not recommended for use in infants under one month of age.

Painful topical treatments on larger surface areas of intact skin:

Adults, including the elderly.

Apply the cream at a dosage of approximately 1.5g to 2g LMX4 /10cm2 skin to be treated, or multiples thereof, up to a maximum area of 900cm2. Apply until response is achieved, which is generally for between 30 to 60 minutes in clinical studies.

Typical estimated larger quantities would be 30g-40g/200cm2 (approximately 10cm x 20cm, or covering a face), 45g-60g/300cm2 (approximately 10cm x 30cm or covering an arm), or 135g-180g/900cm2 (approximately 30cm x 30cm, or covering a torso or back).

Indirect evidence has shown that successive applications of lidocaine-based topical treatments can lead to systemic accumulation of lidocaine. LMX4 must therefore not be reapplied for 12 hours following its removal, giving a maximum of 2 doses in any 24 hour period.

The LMX4 cream should be applied evenly at the specified dosage with a uniform thickness across the area where the topical treatment will occur. Measures may be taken to ensure the cream remains undisturbed until adequate analgesia has been achieved.

Prior to starting the procedure, the LMX4 Cream should be removed using a clean gauze swab and the site for topical treatment prepared in the usual manner. The procedure should be initiated shortly after the cream has been removed.

Use of LMX4 is not recommended for this indication in patients below 18 years of age.

4.3 Contraindications

Hypersensitivity to the active substance, or any of the amide-type local anaesthetics, or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For external use only. Avoid contact with eyes.

Do not apply to irritated skin or if excessive irritation develops. If condition worsens, or if symptoms persist unaltered for more than seven days or clear up and occur again within only a few days, discontinue use of this product and consult a doctor.

Do not use in large quantities over raw or blistered areas.

LMX4 contains 75mg propylene glycol in each 1g. Propylene glycol my cause skin irritation. Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns) without checking with your doctor or pharmacist. Do not use on infants below one month.

LMX4 contains 15mg benzyl alcohol in each 1g. Benzyl alcohol may cause allergic reactions or mild local irritation.

LMX4 contains 7.5mg polysorbate 80 in each 1g. Polysorbates may cause allergic reactions.

LMX4 has not been applied to wounds, mucous membranes or in areas of atopic dermatitis as there are no clinical data in relation to these.

Anaesthetic efficacy during the heel lancing of neonates has not been studied. Application of lidocaine to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine resulting in serious adverse effects.

Studies in laboratory 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. Lidocaine should not be used in any clinical situation in which its penetration or migration beyond the tympanic membrane into the middle ear is possible.

Dermal application of lidocaine may cause transient local blanching followed by transient erythema.

PRECAUTIONS

General: Repeated doses of lidocaine may increase blood levels of lidocaine. Lidocaine should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine including acutely ill, debilitated, or elderly patients.

Lidocaine coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of lidocaine in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine; however, lidocaine should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain. Patients with severe hepatic disease, because of their inability to metabolize local anaesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine.

When lidocaine is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by

scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Lidocaine has bactericidal and antiviral properties in concentrations above 0.5%. For this reason, the results of intra-cutaneous injections of live vaccines (such as BCG vaccination) should be monitored.

Patients treated with Class III anti-arrhythmic drugs (e.g. amiodarone) should be carefully monitored and ECG monitoring considered as cardiac effects may be additive.

4.5 Interaction with other medicinal products and other forms of interaction

Lidocaine should be used with caution in patients receiving Class I anti-arrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and generally synergistic.

Drugs that reduce the clearance of lidocaine (eg cimetidine or betablockers such as propranolol) 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 LMX4) at recommended doses.

The risk of additional systemic toxicity should be considered when large doses of LMX4 are applied to patients already using other local anaesthetics.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine should be used during pregnancy only if clearly needed.

Lidocaine is not contraindicated in labour and delivery. Should LMX4 be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Lidocaine can cross the placental barrier.

Lidocaine is excreted in human milk. Therefore, caution should be exercised when LMX4 is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Common side effects (>1/100) can include irritation, redness, itching, or rash.

In rare cases local anaesthetics have been associated with allergic reactions including anaphylactic shock.

Corneal irritation after accidental eye exposure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose with LMX4 cream is unlikely but signs of systemic toxicity would be consistent with those of lidocaine.

An indication of systemic toxicity may include blurred vision, dizziness or drowsiness, difficulty breathing, trembling, chest pain, or irregular heartbeat.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anaesthetics for topical use, lidocaine, ATC Code: N01BB02

Lidocaine applied to intact skin 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 effecting local anaesthetic action. The onset, depth and duration of dermal analgesia provided by lidocaine depend primarily on the duration of application. LMX4 may cause transient peripheral vasoconstriction followed by transient vasodilation at the application site.

LMX4 has been shown to provide reliable analgesia when applied for between 30 to 60 minutes in clinical studies. The cream may remain on the skin after this time, if adequate analgesia is not achieved. There is limited data available with LMX4 and similar lidocaine-based formulations to show that application times longer than 60 minutes for cannulation procedures and large surface area topical treatments are systemically safe.

5.2 Pharmacokinetic properties

The amount of lidocaine systemically absorbed is directly related to both the duration of application and to the area over which it is applied. It is not known if it is metabolized into the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent to that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats.

Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of concentrations, respectively. The half-life of lidocaine elimination from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, ±24 SD, n=13). This half-life may be increased in cardiac or hepatic dysfunction. More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. The systemic clearance is 10 to 20 mL/min/kg (mean 13, ±3 SD, n=13).

When applied topically to intact skin, the absorption of lidocaine is very low. Increased absorption is therefore to be expected when applied to mucosa or previously damaged skin.

The maximum plasma level of active ingredient was very low (0.3 µ g/ml or less) in a study investigating the application of LMX4 for cannulation in children of different ages. It was well below the toxically effective plasma level of ingredients.

5.3 Preclinical safety data

The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro,* and by mouse micronucleus test *in vivo*. There was no indication in these tests of any mutagenic effects. The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results. The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatic exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/ml). No evidence of genotoxicity was found in the *in vivo* assays measuring unscheduled DNA synthesis in rat hepatocytes, chromosome damage in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts from mice. However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions *in vivo*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl Alcohol

Carbomers
Cholesterol
Phospholipon 80H (Hydrogenated Soy Lecithin)
Polysorbate 80 (Tween 80)
Propylene Glycol
Trolamine
Vitamin E Acetate
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 36 months
Opened: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The pack sizes are 5g and 30g. Both packs comprise either:

- an aluminium tube with an epoxyphenolic internal lacquer, fitted with a polypropylene cap or
- an aluminium tube with a polyamide-imide internal lacquer fitted with a polyethylene 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.
5) A carton containing one 30g tube.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Ferndale Pharmaceuticals Ltd
Unit 740
Thorp Arch Estate
Wetherby
West Yorkshire
LS23 7FX
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20685/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th November 2007
Date of latest renewal: 25th June 2013

10 DATE OF REVISION OF THE TEXT

23/01/2026