483160035

lidocaine/ prilocaine hydrochloride

emla 5% Cream

Local Anaesthesia

1. NAME OF THE MEDICINAL PRODUCT

Lidocaine/ Prilocaine Hydrochloride (Emla) 5% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients:

1 g of Lidocaine/ Prilocaine HCl (Emla) cream contains lidocaine 25 mg and prilocaine 25 mg.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Cream

Lidocaine/ Prilocaine HCl (Emla) cream is an oil-in-water emulsion system in which the oil phase consists of a eutectic mixture of the base forms of lidocaine and prilocaine in the ratio 1:1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Surface anaesthesia of the skin in connection with needle insertion and for superficial surgical procedures.
Surface anaesthesia of leg ulcers prior to cleaning and superficial procedures, e.g. removal of fibrin, pus and necroses.
Surface anaesthesia of the genital mucosa.

4.2 Dosage and method of administration

Adults

Intact skin:

	Dose and Administration	Application Time
for needle insertion e.g. insertion of intravenous cannula, taking of blood samples	½ tube (approx. 2 g) per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.	1 hour; maximum 5 hours
for minor superficial surgical procedures, e.g. curettage of mollusca	1.5-2 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.	1 hour; maximum 5 hours
for more extensive superficial surgical procedures, e.g. split skin grafting	1.5-2 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.	2 hours; maximum 5 hours
on large areas of newly shaven skin (in outpatient care)	Maximum recommended dose: 60 g. Maximum recommended treatment area: 600 cm^2	1 hour; maximum 5 hours

Leg ulcers:

For cleaning of leg ulcers: approx. 1-2 g per 10 cm^2. The cream is applied in a thick layer to the surface of the ulcer, but not more than 10 g per treatment occasion. Cover the ulcer surface with an occlusive dressing. An opened tube is intended for single use, and left-over cream should therefore be discarded after each treatment occasion.

Application time: at least 30 minutes.

For leg ulcers with tissue that is especially difficult to penetrate, the application time may be extended to 60 minutes. Cleaning of the ulcer should be commenced within 10 minutes of removal of the cream.

Lidocaine/ Prilocaine HCl (Emla) has been used for up to 15 treatment occasions during a 1-2 month period without a reduction in effect or increase in the number of local reactions.

Genital use

Skin:

Use before injection of local anaesthetics:

Men: 1 g per 10 cm^2. A thick layer of cream is applied to the skin.

Application time: 15 minutes.

Women: 1-2 g per 10 cm^2. A thick layer of cream is applied to the skin.

Application time: 60 minutes.

Mucosa:

For removal of condyloma or before injection of local anaesthetics: approx. 5-10 g, depending on the area to be treated. The whole surface, including mucous membrane folds must be covered.

Occlusion is not necessary.

Application time: 5-10 minutes.

The procedure should be commenced immediately after removal of the cream.

Children

For needle insertion, curettage of mollusca and other minor superficial surgical procedures: 1 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing. The dose should not exceed **1 gram per 10 cm^2** and should be adjusted according to the application area.

Age	Application Area	Application Time
0-3 months	maximum 10 cm^2 (total of 1 g) *(maximum daily dose)*	1 hour *(note: no longer)*
3-12 months	maximum 20 cm^2 (total of 2 g)	1 hour
1-6 years	maximum 100 cm^2 (total of 10 g)	1 hour; maximum 5 hours
6-12 years	maximum 200 cm^2 (total of 20 g)	1 hour; maximum 5 hours

Children with atopic dermatitis: reduced application time to 30 minutes.

4.3 Contraindications

Known hypersensitivity to local anaesthetics of the amide type or to any of the excipients. Lidocaine/ Prilocaine HCl (Emla) may not be used in premature infants (born before 37 completed weeks of pregnancy).

4.4 Special warnings and special precautions for use

When Lidocaine/ Prilocaine HCl (Emla) is used as recommended for adults, the formation of methaemoglobin as a result of metabolites of prilocaine is not normally a clinical problem. However, some patients are more susceptible to drug-induced methaemoglobinaemia, such as patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia.

Lidocaine/ Prilocaine HCl (Emla) must be used with care near the eyes, since it can cause irritation in the eyes. In addition, the loss of protective reflexes may allow the occurrence of corneal irritation and potential abrasion. If Lidocaine/ Prilocaine HCl (Emla) comes into contact with the eyes, the eye should be rinsed immediately with water or sodium chloride solution, and protected until sensation returns.

Caution in cases of use on skin with atopic dermatitis. The application time should be reduced (to 15-30 minutes).

Studies have not been able to show that Lidocaine/ Prilocaine HCl (Emla) provides pain relief during the heel lancing of neonates.

Safety and efficacy in children under 3 months have only been studied with administration of a single dose. In these children, a transient increase in the methaemoglobin level is often seen for up to 13 hours after Lidocaine/ Prilocaine HCl (Emla) has been applied. However, the increases observed are probably of no clinical significance.

Lidocaine/ Prilocaine HCl (Emla) should not be used on damaged tympanic membrane or in other situations where penetration to the middle ear may occur. Lidocaine/ Prilocaine HCl (Emla) should not be applied to open sores. Lidocaine/ Prilocaine HCl (Emla) should not be used on the genital mucosa of children on account of incomplete data regarding absorption.

Lidocaine and prilocaine have bactericidal and antiviral properties in concentrations above 0.5-2 %. Therefore the results of intracutaneous injections of live vaccine (e.g. BCG) should be carefully monitored.

Until further clinical experience has been obtained, Lidocaine/ Prilocaine HCl (Emla) should not be used on children aged 0-12 months who are being treated concomitantly with methaemoglobin-inducing drugs (see also Sec. 4.9).

Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be closely observed and ECG monitoring should be considered, as the cardiac effects of lidocaine when administered concomitantly with class III anti-arrhythmic drugs may be additive.

4.5 Interaction with other medicinal products and other forms of interaction

Lidocaine/ Prilocaine HCl (Emla) can increase the formation of methaemoglobin in patients treated with some methaemoglobin-inducing drugs (e.g. sulfa preparations).

With high doses of Lidocaine/ Prilocaine HCl (Emla), the risk of additive systemic effects should be taken into account in patients who are given local anaesthetics or preparations that are structurally similar to local anaesthetics, e.g. tocainide.

No specific interaction studies with local anaesthetics and class III anti-arrhythmic drugs (e.g. amiodarone) have been carried out, but caution is recommended (see also Sec. 4.4).

Medicinal products that reduce the clearance of lidocaine (e.g. cimetidine or beta-blockers) may cause potentially toxic plasma levels when lidocaine is given in repeated high doses for prolonged periods of time. Such interactions are not clinically significant in short-term treatment with lidocaine at recommended doses.

4.6 Pregnancy and lactation

Pregnancy

There is insufficient data regarding treatment of pregnant women with lidocaine and prilocaine.

Lidocaine and prilocaine cross the placenta. It is reasonable to assume that lidocaine and prilocaine have been used by a large number of pregnant women and women of child-bearing age. There are no indications that lidocaine and prilocaine may cause disturbances in the reproductive process such as an increased frequency of malformations or direct or indirect effects on the foetus. However, the risks for humans have not been fully assessed.

Animal studies are incomplete with regards to effects of lidocaine and prilocaine on pregnancy, embryonal/foetal development, parturition and development after birth (see Sec. 5.3).

In temporary use during pregnancy the benefits are considered to compensate for the possible risks.

Lactation

Lidocaine and prilocaine are excreted into breast milk in small amounts. An effect on the child appears unlikely with recommended doses. Breastfeeding can therefore be continued during treatment with Lidocaine/ Prilocaine HCl (Emla).

4.7 Effects on ability to drive and use machines

Reaction capacity is not affected by treatment with Lidocaine/ Prilocaine HCl (Emla).

4.8 Undesirable effects

Adverse reactions with local anaesthetics in the true sense of the term occur in less than 1/1000 those treated.

Common (≥1/100, <1/10)	*General disorders and administration site conditions:* Transient local skin reactions at the application site such as local paleness, redness, oedema.
Uncommon (≥1/1 000, <1/100)	*General disorders and administration site conditions:* Initially slight burning sensation, itching (at the application site).
Rare (≥1/10 000, <1/1000)	*General disorders and administration site conditions:* Allergic reactions, in the most severe cases anaphylactic shock. Methaemoglobinaemia (see sections 4.5 and 4.9).

Rare cases of mild reactions at the application site, such as purpura or petechiae, have been reported, especially after prolonged application times in children with atopic dermatitis or mollusca. In cases of accidental contact with the eye, corneal irritation can occur.

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4.9 Overdosage

Systemic toxicity is very unlikely with normal use of Lidocaine/ Prilocaine HCl (Emla). In the possible event of toxicity, the symptoms are expected to be similar to those seen after local anaesthetic treatment, i.e. excitatory CNS symptoms and in severe cases CNS depression and myocardial depression.

Rare cases of clinically significant methaemoglobinemia have been reported (see Sec. 4.8). Prilocaine in high doses can increase the methaemoglobin level.

Topical administration of 125 mg prilocaine for 5 hours caused moderate methaemoglobinemia in a 3-month-old child. Topical administration of 8.6-17.2 mg/kg lidocaine caused very severe intoxication in babies.

Severe neurological symptoms (convulsions, CNS depression) require symptomatic treatment such as assisted ventilation and anticonvulsant drugs. For methaemoglobinaemia, the antidote is methylthione. Due to slow systemic absorption, a patient with symptoms of toxicity should be observed for several hours after treatment of these symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics
ATC code: N01BB20

Lidocaine/ Prilocaine HCl (Emla) cream contains lidocaine and prilocaine, which are local anaesthetics of the amide type. On penetration into the epidermis and dermis, these substances produce anaesthesia of the skin. The degree of anaesthesia depends on the application time and dose.

Intact skin

With an application time of 1-2 hours the effect lasts for approximately two hours after the occlusive dressing has been removed.

In clinical trials with Lidocaine/ Prilocaine HCl (Emla) on intact skin, no differences with regard to safety or efficacy (including time to anaesthesia) could be seen between geriatric patients (65-96 years) and younger patients.

The superficial vascular bed is affected by Lidocaine/ Prilocaine HCl (Emla), and this can cause transient paleness or redness. This reaction occurs more rapidly in atopic dermatitis, after only 30-60 minutes, indicating more rapid absorption through the skin (see also Sec. 4.4).

A study in healthy volunteers with intact skin shows that in 90% the anaesthesia is sufficient for use for biopsy punches (4 mm in diameter) to a depth of 2 mm, after a 60-minute application time and to a depth of 3 mm after a 120-minute application time.

Lidocaine/ Prilocaine HCl (Emla) is equally effective, irrespective of the colour/ pigmentation of the skin (skin types I-VI).

Lidocaine/ Prilocaine HCl (Emla) can be used prior to vaccination with subcutaneous or intramuscular vaccine. For intracutaneous vaccination with live vaccine, e.g. BCG, see section 4.4.

Genital mucosa

The time to onset of action for necessary anaesthesia is shorter, as absorption takes place more rapidly than in cases of application to intact skin.

After a 5 to 10-minute application of Lidocaine/ Prilocaine HCl (Emla) to the genital mucosa in women, the local anaesthesia for aragon laser-induced pain lasted for 15-20 minutes (with an inter-individual variation from 5-45 minutes).

Leg ulcers

No negative effect on ulcer healing or bacterial flora has been observed.

For cleaning leg ulcers, Lidocaine/ Prilocaine HCl (Emla) provides pain relief for up to 4 hours after application.

5.2 Pharmacokinetic properties

The systematic absorption of Lidocaine/ Prilocaine HCl (Emla) depends on the amount of cream, the application time, the thickness of the skin (this varies in different areas of the body) and the condition of the skin in other respects such as skin diseases (e.g. absorption increases in atopic dermatitis, see Sec. 4.4) and shaving. When used on leg ulcers, the characteristics of the leg ulcer can affect absorption, e.g. absorption increases with increased size of the leg ulcer.

Intact skin.

After application of 60 g Lidocaine/ Prilocaine HCl (Emla) cream per 400 cm^2 (1.5 g per 10 cm^2) for 3 hours to intact skin (thigh) in adults, the systemic absorption has been measured as being 3% for lidocaine and 5% for prilocaine. Absorption takes place slowly. With the above-mentioned dose, maximum plasma concentrations for lidocaine (mean 0.12 mcg/mL) and prilocaine (mean 0.07 mcg/mL) were reached within approximately 4 hours after application. Only at levels of 5-10 mcg/mL is there a risk of toxic symptoms. In this case, shaving of the skin took place 8-12 hours before the application of the cream.

Leg ulcers.

After application to leg ulcers of 5-10 g Lidocaine/ Prilocaine HCl (Emla) for 30 minutes to leg ulcers, maximum plasma levels of lidocaine and prilocaine were reached after approximately 1-2.5 hours (for lidocaine within the range 0.05-0.84 mcg/mL and for prilocaine 0.02 - 0.08 mcg/mL).

After repeated application of Lidocaine/ Prilocaine HCl (Emla) to leg ulcers, no relevant accumulation in plasma of lidocaine, prilocaine or their metabolites was observed. 2-10 g Lidocaine/ Prilocaine HCl (Emla) was applied for 30-60 minutes to a maximum area of 62 cm^2, for a total of 15 times in 1 month, 3-7 occasions per week.

Genital mucosa.

After application of 10 g Lidocaine/ Prilocaine HCl (Emla) cream to the vaginal mucosa for 10 minutes, maximum plasma concentrations (mean values: lidocaine 0.18 mcg/mL, prilocaine 0.15 mcg/mL) were measured after approximately 35 minutes.

5.3 Preclinical safety data

Reproduction toxicology

Lidocaine
In studies of embryonic/foetal development in which rats or rabbits were treated during the period of organogenesis no teratogenic effects were seen. Embryonal toxicity was observed in rabbits at mother toxic dose. The offspring to rats treated with mother toxic dose during late pregnancy and lactation showed decreased postnatal survival.

Prilocaine
Reproduction toxicological studies with prilocaine are incomplete.

In a combination study in which prilocaine and lidocaine were given to pregnant rats during the period of organogenesis, no effects on embryonic/foetal development were seen. There is, however, a lack of data on systemic exposure for comparison with clinical exposure.

Genotoxicity and carcinogenicity

Lidocaine
Genotoxicity tests with lidocaine were negative. The carcinogenicity of lidocaine has not been studied. Lidocaine's metabolite 2,6-xylidine (also called 2,6-dimethylaniline) has genotoxic potential *in vitro*. Tumours in the nasal cavity, subcutis and liver were seen in a carcinogenicity study in rats with an exposure to 2,6-xylidine in utero, post-natally and for the entire life cycle. The clinical relevance of the tumour findings during short-term/intermittent use of lidocaine is unknown.

Prilocaine
Genotoxicity studies with prilocaine were negative. The carcinogenicity of prilocaine has not been studied. Prilocaine's metabolite ortho-toluidine has genotoxic potential *in vitro*. In carcinogenicity studies of ortho-toluidine in rats, mice and hamsters, tumours were seen in several organs. The clinical relevance of the tumour findings in short-term/intermittent use of prilocaine is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer, macrogolglycerol hydroxystearate, sodium hydroxide to pH 8.7-9.7, water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to the outer carton/aluminum tube.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Do not freeze.

6.5 Availability

Collapsible tube of aluminum, internally coated with protective lacquer.
Lidocaine/ Prilocaine HCl (Emla) 5% Cream – 5 g Tube (Box of 5's)

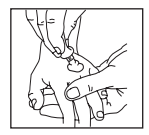
DR-XY3694

6.6 Special instructions for use, handling and disposal

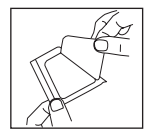
Information for the user and instructions for use are contained in every pack. Use the tube cap to puncture the membrane over the tip of the tube.

INSTRUCTIONS FOR APPLICATION

1. Press out a sufficient quantity of the cream (about 2 g or 1/2 of 5 g tube) at the site of the procedure. Note well specific instructions for children younger than one year.

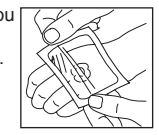


2. Take one of the enclosed occlusive dressings and remove the center cut-out-piece.



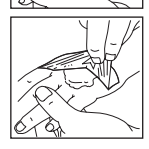
3. Peel the paper liner from the paper framed dressing.

4. Cover the Lidocaine/ Prilocaine HCl (Emla) cream so that you get a thick layer underneath. Do not spread out the cream. Smooth down the dressing edges carefully to avoid leakage.



5. Remove the paper frame. The time of application can easily be marked directly on the occlusive dressing. Note well, Lidocaine/ Prilocaine HCl (Emla) cream must be applied at least 1 - 2 hours before the start of the procedure and may be left on for several hours with remaining effect.

6. Remove the occlusive dressing, wipe off the Lidocaine/ Prilocaine HCl (Emla) cream, clean the entire area with alcohol and prepare the patient for the procedure. Duration of effective skin anaesthesia will be approximately 2 hours after removal of the occlusive dressing.



CAUTION
Foods, Drugs and Devices, and Cosmetics Act prohibits dispensing without prescription. For suspected adverse drug reaction, report to the FDA at www.fda.gov.ph and to Aspen Philippines at APH.PV.Phils@ph.aspenpharma.com. The patient should seek medical attention immediately at first sign of any adverse drug reaction.

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