1. NAME OF THE MEDICINAL PRODUCT

EMLA 5% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lidocaine 2.5%
Prilocaine 2.5%
For excipients, see 6.1

3. PHARMACEUTICAL FORM

White soft homogeneous cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical anesthesia for superficial dermal analgesia in connection with insertion of IV catheters, blood sampling and superficial surgical procedures.

4.2 Posology and method of administration

Surface/ Age	**Procedure**	**Application**
Skin		Apply a thick layer of cream on the skin and cover it with occlusive dressing.
Adults		Approx. 1.5 g/10 cm^2
	Minor procedures e.g. needle insertion and surgical treatment of localised lesions.	2 g (approx. half a 5 g tube) for 1 to 5 hours[1)]
	Dermal surgical procedures on larger areas in a hospital setting e.g. split skin grafting.	Approx. 1.5-2 g/10 cm^2 for 2 to 5 hours[1)]
	Dermal procedures on newly shaven skin of large body areas e.g. laser hair removal (self-application by patient)	Maximum recommended dose: 60g. Maximum recommended treated area: 600 cm^2 for a minimum of 1 hour, maximum 5 hours.[1)]
Children	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions	Approx. 1.0 g/10 cm^2 for 1 hour (see details below)
Neonates 0-3 months[3) 8)]		Up to 1.0 g and 10 cm^2 for one hour [2)]
Infants 3-12 months[3)]		Up to 2.0 g and 20 cm^2 for 1-4 hours [4)]

Children 1-6 years		Up to 10.0 g and 100 cm^2 for 1-4 hours[1)]
Children 7-12 years		Up to 20.0 g and 200 cm^2 for 1-4 hours[1)]
Children with atopic dermatitis	Prior to removal of mollusca.	Application time: 30 minutes
Genital mucosa Adults	Surgical treatment of localised lesions, e.g. removal of genital warts (condylomata accuminata) and prior to injection of local anaesthetics.	Approx. 5-10 g EMLA for 5-10 minutes[1)]. No occlusive dressing is required. Commence the procedure immediately after removal of cream.
	Prior to cervical curettage.	Administer 10 g of cream in lateral vaginal fornices for 10 minutes.
Skin of male genital organs Adults	Prior to injection of local anaesthetics	Apply a thick layer of EMLA cream (1 g/10cm^2) with occlusive dressing for 15 minutes
Skin of female genital organs Adults	Prior to injection of local anaesthetics[7)]	Apply a thick layer of EMLA cream (1-2 g/10cm^2) with occlusive dressing for 60 minutes
Leg ulcer Adults	Mechanical cleansing /debridement of leg ulcer(s).	Apply a thick layer of the cream, approx. 1-2 g/10 cm^2 up to a total of 10 g to the leg ulcer(s).[5, 6)] Cover with an occlusive dressing. Application time: 30 to 60 minutes. Cleansing should start without delay after removal of the cream.

1) After a longer application time anaesthesia decreases.

2) Application for >1 hour has not been documented.

3) Until further clinical data are available, EMLA should not be used in infants up to 12 months of age receiving treatment with methaemoglobin-inducing agents. 4) No clinically significant increase in plasma methaemoglobin levels has been observed after an application time of up to 4 hours on 16 cm^2.

5) EMLA has been used for the treatment of leg ulcers up to 15 times over a period of 1-2 months without loss of efficacy or increased number or severity of adverse events. 6) Plasma levels have not been determined in patients treated with doses of >10 g, (See also Section 5.2).

7) On female genital skin, EMLA alone applied for 60 or 90 min does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.

8) Until further clinical data are available, EMLA should not be used at less than 37 weeks gestational age.

One gram of EMLA cream pressed out of a tube of 30 g is approximately 3.5 cm. Persons frequently applying or removing cream should ensure that contact is avoided in order to prevent the development of hypersensitivity.

Paediatric population

Adolescents ≥ 12 years:

As for adults (approximately 2 g EMLA applied under an occlusive dressing for a minimum of 60 minutes, maximum 5 hours).

Term newborn infants, infants and children ≤ 11 years:

In term newborn infants and infants < 3 months, only one single dose should be applied in any 24 hour period.

For children aged 3 months and above, a maximum of 2 doses, separated by at least 12 hours can be given within any 24 hour period. If, based on clinical need, a decision is nevertheless taken to use two applications in children under the age of 3 months, see sections 4.4 and 4.8.

The safety of EMLA in pre-term newborn infants has not been established. Use of EMLA is not recommended in pre-term infants.

Use of EMLA is not recommended in infants less than 3 months of age receiving treatment with methaemoglobin-inducing drugs (see section 4.4).

For all age groups analgesic efficacy may decline if the skin application time is more than 5 hours. Procedures on intact skin should begin soon after the occlusive dressing is removed.

On the genital mucosa analgesic efficacy declines after 10-15 minutes and therefore the procedure should be commenced immediately.

Methods of dose estimation

If high levels of accuracy in dosing are required to prevent overdose (i.e. at doses approaching the maximum in neonates or if two applications may be required in a 24 h period), a syringe can be used where 1 ml = 1 g.

A string of cream can be used to define the quantity of EMLA administered from the 30 g tube where 1 g = 3.5 cm; however, a string of cream may not be appropriate for all application needs, e.g. when administering a low dose to small surface areas.

4.3 Contraindications

Hypersensitivity to the active substances (lidocaine and/or prilocaine) or local anaesthetics of the amide type or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

EMLA should not be used in the following cases:

(a) in pre-term neonates i.e. gestational age less than 37 weeks.

(b) in infants/neonates between 0 and 12 months of age receiving treatment with methaemoglobin-inducing agents due to the possible additive effects.

In infants/neonates younger than 3 months a transient, clinically insignificant increase in methaemoglobin level is commonly observed up to 12 hours after an application of EMLA.

Patients with defective glucose-6-phosphate dehydrogenase, hereditary or idiopathic methaemoglobinaemia are more susceptible to active-substance-induced signs of methaemoglobinaemia.

In glucose-6-phosphate dehydrogenase deficient patients the antidote methylene blue is ineffective at methaemoglobin reduction, and is capable of oxidising haemoglobin itself, and therefore methylene blue therapy cannot be given.
In term newborn infants, infants and children, EMLA should only be used on intact skin and should not be applied to genital mucosa.

In term neonates and infants < 3 months, only one single dose should be applied in any 24 hour period. If, based on clinical need, a decision is nevertheless taken to use two applications in children under the age of 3 months, the child should be clinically monitored for systemic adverse reactions (see sections 4.8 and 4.9).

Due to insufficient data on absorption, EMLA Cream should not be applied to open wounds (excluding leg ulcers).

Due to the potentially enhanced absorption on newly shaven skin, it is important to adhere to the recommended dosage, area and time of application (see section 4.2). Studies have been unable to demonstrate the efficacy of EMLA for heel lancing in neonates.

EMLA should not be applied to the genital mucosa of children owing to insufficient data on absorption of active substances. However, when used in neonates for circumcision, a dose of 1.0 g EMLA on the prepuce has been proven to be safe.

Care should be taken when applying EMLA Cream to patients with atopic dermatitis. A shorter application time, 15-30 minutes, may be sufficient (see section 5.1). Application times of longer than 30 minutes in patients with atopic dermatitis may result in an increased incidence of local vascular reactions, particularly application site redness and in some cases petechia and purpura (see section 4.8). Prior to removal of mollusca in children with atopic dermatitis, it is recommended to apply cream for 30 minutes.

When applied in the vicinity of the eyes, EMLA cream should be used with particular care since it may cause eye irritation. Also the loss of protective reflexes may allow corneal irritation and potential abrasion. If eye contact occurs, the eye should immediately be rinsed with water or sodium chloride solution and protected until sensation returns.

EMLA Cream should not be applied to an impaired tympanic membrane. Tests on laboratory animals have shown that EMLA cream has an ototoxic effect when instilled into the middle ear. Animals with an intact tympanic membrane, however, show no abnormality when exposed to EMLA cream in the external auditory canal.

Patients treated with anti-arrhythmics of class III (e.g., amiodarone) should be carefully monitored and ECG monitoring considered, as cardiac effects may be additive.

Lidocaine and prilocaine have bacteriocidal and antiviral properties in concentrations above 0.5 – 2%. For this reason, although one clinical study suggests that the immunisation response, as assessed by local wheal formation, is not affected when EMLA Cream is used prior to BCG vaccination, the results of intracutaneous injections of live vaccines should be monitored.

EMLA Cream contains macrogolglycerol hydroxystearate, which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Prilocaine in high doses may cause an increase in methaemoglobin levels particularly in conjunction with methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofurantoin, phenytoin, phenobarbital). This list is not exhaustive.

With large doses of EMLA Cream, consideration should be given to the risk of additional systemic toxicity in patients receiving other local anaesthetics or medicinal products structurally related to local anaesthetics, since the toxic effects are additive.

Specific interaction studies with lidocaine/prilocaine and anti-arrhythmics class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

Medicinal products that reduce the clearance of lidocaine (e.g., cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long time period.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although topical application is associated with only a low level of systemic absorption, the use of EMLA Cream in pregnant women should be undertaken with care because insufficient data are available concerning the use of EMLA Cream in pregnant women. However, animal studies do not indicate any direct or indirect negative effects on pregnancy, embryo-foetal development, parturition or postnatal development. Reproduction toxicity has been shown with subcutaneous/intramuscular administration of high doses of lidocaine or prilocaine much exceeding the exposure from topical application (see section 5.3).

Lidocaine and prilocaine cross the placental barrier and may be absorbed by the foetal tissues. It is reasonable to assume that lidocaine and prilocaine have been used in a large number of pregnant women and women of childbearing age. No specific disturbances to the reproductive process have so far been reported, e.g. an increased incidence of malformations or other directly or indirectly harmful effects on the foetus.

Breast-feeding

Lidocaine and, in all probability, prilocaine are excreted into breast milk, but in such small quantities that there is generally no risk of the child being affected at therapeutic dose levels. EMLA Cream can be used during breast-feeding if clinically needed.

Fertility
Animal studies have shown no impairment of the fertility of male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

EMLA Cream has no or negligible influence on the ability to drive and use machines when used at the recommended doses.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) are related to administration site conditions (transient local reactions at the application site), reported as common.

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with EMLA Cream therapy is tabulated below. The table is based on adverse events reported during clinical trials, and/or post-marketing use. Their frequency of Adverse Reactions is listed by MedDRA System Organ Class (SOC) and at the preferred term level.

Within each System Organ Class, adverse reactions are listed under frequency categories of: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic system disorders			Methaemoglobinaemia[1]
Immune system disorders			Hypersensitivity[1, 2, 3]
Eye disorders			Corneal irritation[1]
Skin and subcutaneous tissue disorders			Purpura[1], Petechiae[1] (especially after longer application times in children with atopic dermatitis or mollusca contagiosa)
General disorders and administration site conditions	Burning sensation[2, 3] Application site pruritus[2, 3]	Burning sensation[1] Application site irritation[3]	

	Application site erythema[1, 2, 3] Application site oedema[1, 2, 3] Application site warmth[2, 3] Application site pallor[1, 2, 3]	Application site pruritus[1] Application site paraesthesia[2] such as tingling Application site warmth[1]	

[1]Skin

[2]Genital Mucosa

[3]Leg ulcer

Paediatric population

In clinical trials 298 neonates and infants aged up to 12 months were treated with EMLA (Table 3). A large number of infants and children aged 1 year and older have been treated with EMLA in clinical trials and in clinical practice since 1984. **Table 3. Number of paediatric patients, up to 12 months old, included in clinical studies with EMLA, by age group**

Group	Number of patients
Pre-term neonates	21
Age 0–1 months	148
Age 1–3 months	55
Age 3–12 months	74
Total number	**298**

Frequency, type and severity of adverse reactions are similar in the paediatric and adult age groups, except for methaemoglobinaemia, which is more frequently observed, often in connection with overdose, in neonates and infants aged 0 to 12 months.

Rare cases of clinically significant methaemoglobinaemia in children have been reported in literature. Prilocaine, one of the components of EMLA, may in high doses cause an increase in the methaemoglobin level, particularly in susceptible individuals (Section 4.4) and in conjunction with other methaemoglobin-inducing agents. Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylthioninium chloride (Section 4.9).

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
Additionaly, you can also report to Padagis via the following address: Padagis.co.il

4.9 Overdose

Rare cases of clinically significant methaemoglobinaemia have been reported. Prilocaine in high doses may cause an increase in methaemoglobin levels particularly in conjunction with methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofurantoin, phenytoin and phenobarbital). Consideration should be given to the fact that pulse oximeter values may overestimate the actual oxygen saturation in case of increased methaemoglobin fraction; therefore, in cases of suspected methaemoglobinaemia, it may be more helpful to monitor oxygen saturation by co-oximetry.

Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylene blue (see also section 4.4).

Should other symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes of administration. Local anaesthetic toxicity is manifested by symptoms of nervous system excitation and, in severe cases, central nervous and cardiovascular depression. Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive medicinal products; circulatory signs are treated in line with recommendations for resuscitation.

Since the rate of absorption from intact skin is slow, a patient showing signs of toxicity should be kept under observation for several hours following emergency treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics, local; amides

ATC code: N01B B20

Mechanism of action

EMLA Cream provides dermal anaesthesia through the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and the vicinity of dermal pain receptors and nerve endings.

Lidocaine and prilocaine are amide-type local anaesthetics. They both stabilise neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of

impulses, thereby producing local anaesthesia. The quality of anaesthesia depends upon the application time and the dose.

Skin

In patients with atopic dermatitis, a similar but shorter vascular reaction is seen, with erythema occurring after 30-60 minutes, indicating more rapid absorption through the skin (see section 4.4).

Genital mucosa

Absorption from the genital mucosa is more rapid and onset time is shorter than after application to the skin.

Paediatric population

Clinical safety studies

Methaemoglobin formation after the use of EMLA in term infants was studied with the aim to establish the safety of 1 g EMLA Cream 5%. Forty-seven neonates and infants, aged 0-3 months, with a post conceptual age of ≥37 weeks were included in a double blind, randomized, placebo-controlled study. Methaemoglobin concentrations before treatment with EMLA and placebo were in the range 0.67-1.57% and 0.50- 1.53%, respectively. After treatment with 1 g EMLA/placebo for 60-70 min methaemoglobin concentrations were 0.50-2.53% for EMLA and 0.50-1.53% for placebo. From 3.5 to 13 h after application the concentrations were significantly higher with EMLA than with placebo, but were clinically insignificant. One sample, in the EMLA group (2.53%), had a methaemoglobin concentration above the reference value of 2%.

Altogether, data from eleven clinical studies in neonates and infants showed that peak methaemoglobin concentrations occur about 8 hours after epicutaneous EMLA administration, are clinically insignificant with recommended dosage, and return to normal values after about 12-13 hours. Methaemoglobin formation is related to the cumulative amount of prilocaine percutaneously absorbed, and may therefore increase with prolonged application times of EMLA.

Physiological methaemoglobin concentrations in both paediatric patients and adults are normally maintained below 2%. A major increase in methaemoglobin (to a concentration of 25-30%) will cause signs and symptoms of hypoxaemia. In neonates elevated methaemoglobin levels up to 5–6% are not regarded as clinically significant.

Circumcision

In two randomized, double-blind, placebo-controlled studies in full-term neonates aged 1 to 4 days EMLA Cream (0.5 or 1 g) was applied on the prepuce for one hour before circumcision, covered with an occlusive dressing. In the study using 0.5 g EMLA there was no significant differences with placebo in assessment of pain performed by evaluating facial expressions or heart rate, respiratory rate, oxygen saturation, nor in general skin colour.

EMLA Cream (1 g) significantly reduced the pain during parts of the circumcision procedure, as demonstrated by less facial activity, reduction in duration of cry and lower heart rates. No differences were found for oxygen saturation, respiratory rate and Neonatal Infant Pain Scale (NIPS) – which includes facial expression, cry, breathing pattern and state of arousal.

Vaccination
Two randomized double-blind, placebo-controlled studies in infants and neonates looked at anaesthetic efficacy of EMLA Cream in vaccinations and the effect on the immunogenicity of live vaccines.

The first study used EMLA Cream prior to subcutaneous measles-mumps-rubella vaccine, in patients aged 12-15 months, where 1g of cream was applied for 60-180 minutes. EMLA significantly reduced vaccination pain versus placebo, demonstrated by difference between the pre- and post-vaccination total score on the Modified Behavioural Pain Scale (MBPS - includes measurement of facial expression, cry and body movement). No difference versus placebo was seen with the separate assessment of proportion of patients that cry and duration of cry.
The second used EMLA Cream prior to intramuscular diptheria-pertussis-tetanusinactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines in patients aged 0-6 months, where 1 or 2g of cream was applied to patients aged 0-4 and 6 months respectively, for 60-180 minutes. EMLA significantly reduced vaccination pain versus placebo, demonstrated as above, for the 6 month-old group, however in the 0-4 month old group there was high variation in treatment response. In the 2 and 4 month-old groups, EMLA gave reduced pain versus placebo, however statistical significance was not shown (p=0.120 and 0.225 respectively).

Within both studies, the use of EMLA did not affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared to placebo treated patients.

5.2 Pharmacokinetic properties

Systemic absorption of lidocaine and prilocaine from EMLA Cream is dependent upon the dose, application time, and the thickness of the skin, which varies between different areas of the body.

Intact skin: In order to provide reliable dermal analgesia, EMLA Cream should be applied under an occlusive dressing for at least 1 hour. The duration of analgesia after an application time of 1-2 hours is at least 2 hours after removal of the dressing.

After the application of EMLA Cream to intact male genital skin for 15 minutes (median 1g), plasma concentrations of lidocaine and prilocaine (mean 6.6 nanogram/ml and 4.1 nanogram/ml) were reached after approximately 1.5 hours.

After application to the thigh in adults (60 g cream/400 cm^2 for 3 hours) the extent of absorption was approximately 5% of lidocaine and prilocaine. Maximum plasma

concentrations (mean 0.12 and 0.07 μg/ml) were reached approximately 2-6 hours after the application.

The extent of systemic absorption was approximately 10% following application to the face (10 g/100 cm^2 for 2 hours). Maximum plasma levels (mean 0.16 and 0.06 μg/ml) were reached after approximately 1.5-3 hours.

Genital mucosa

After the application of 10 g EMLA Cream for 10 minutes to vaginal mucosa, maximum plasma concentrations of lidocaine and prilocaine (mean 0.18 μg/ml and 0.15 μg/ml respectively) were reached after 20-45 minutes.

Paediatric population

*Follow*ing the application of 1 g EMLA Cream in infants/neonates below 3 months of age, to approx 10 cm^2 for one hour, the maximum plasma concentrations of lidocaine and prilocaine were 0.135 micrograms/ml and 0.107 micrograms/ml respectively.

Following the application of 2 g EMLA Cream in infants between 3 and 12 months of age, to approx 16 cm^2 for four hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.155 micrograms/ml and 0.131 micrograms/ml respectively.

Following the application of 10 g of EMLA Cream in children between 2 and 3 years of age, to approx 100 cm^2 for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.315 micrograms/ml and 0.215 micrograms/ml respectively.

Following the application of 10-16 g EMLA Cream in children between 6 and 8 years of age, to approx 100-160 cm^2 for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.299 micrograms/ml and 0.110 micrograms/ml respectively.

5.3 Preclinical safety data

Lidocaine and prilocaine are well established active ingredients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate, Carbomer 974P, sodium hydroxide, water purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 4 weeks.

6.4 Special precautions for storage

Store below 30°C, do not freeze.

6.5 Nature and contents of container

Aluminum tube with Epoxy resin inner coating. Synthetic rubber sealing ring. Cap with spike for perforation. EMLA Cream is available in tubes of 30 g.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

Persons frequently applying or removing cream should ensure that contact is avoided in order to prevent the development of hypersensitivity.

7. REGISTRATION HOLDER

Padagis Israel Agencies Ltd, 1 Rakefet St., Shoham.

8. MANUFACTURER

Recipharm Karlskoga AB, Karlskoga, Sweden for Aspen.

9. MARKETING AUTHORISATION NUMBER

043-25-25706-00

Revised in June 2023 according to MOH guidelines.

5.6.23