Annex III

Summary of product characteristics, labelling and package leaflet

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EMLA and associated names (see Annex I) 25mg/g + 25mg/g cream
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

Cream
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMLA Cream is indicated for:

- Topical anaesthesia of the skin in connection with:
  - needle insertion, e.g. intravenous catheters or blood sampling;
  - superficial surgical procedures;

in adults and in the paediatric population

- Topical anaesthesia of the genital mucosa, e.g. prior to superficial surgical procedures or infiltration anaesthesia; in adults and adolescents ≥12 years

- Topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement in adults only

4.2 Posology and method of administration

Posology
Adults and adolescents
The details of the Indications or Procedures for use, with Dosage and Application Time are provided in Tables 1 and 2.
For further guidance on the appropriate use of the product in such procedures, please refer to *Method of administration*.

Table 1 Adults and adolescents 12 years of age and above

Indication/Procedure	**Dosage and Application Time**
Skin	
Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	2 g (approx. half a 5 g tube) or approx. 1.5g/10 cm^2 for 1 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: 60 g. Maximum recommended treated area; 600 cm^2 for a minimum of 1 hour, maximum 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)].
Skin of male genital organs Prior to injection of local anaesthetics	1 g/10 cm^2 for 15 minutes

Skin of female genital organs Prior to injection of local anaesthetics[2)]	1-2 g/10 cm^2 for 60 minutes
Genital mucosa	
Surgical treatment of localised lesions, e.g. removal of genital warts (condylomata acuminata) and prior to injection of local anaesthetics	Approx. 5-10 g of cream for 5-10 minutes[1) 3) 4)].
Prior to cervical curettage	10 g of cream should be administered in the lateral vaginal fornices for 10 minutes.
Leg ulcer(s)	
Adults only Mechanical cleansing/debridement	Approx. 1-2 g/10 cm^2 up to a total of 10 g to the leg ulcer(s)[3) 5)]. Application time: 30-60 minutes.

[1)] After a longer application time anaesthesia decreases.
[2)] On female genital skin, EMLA alone applied for 60 or 90 minutes does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.
[3)] Plasma concentrations have not been determined in patients treated with doses of >10 g (see also Section 5.2).
[4)] In adolescents weighing less than 20 kg the maximum dose of EMLA on genital mucosa should be proportionally reduced.
[5)] EMLA has been used for the treatment of leg ulcers up to 15 times over a period of 1 to 2 months without loss of efficacy or increased number or severity of adverse events.

Paediatric population

Table 2 Paediatric patients 0-11 years of age

Age group	Procedure	Dosage and Application time
	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Approx. 1g/10 cm^2 for one hour (see details below)
Newborn infants and infants 0-2 months[1) 2) 3)]		Up to 1 g and 10 cm^2 for one hour[4)]
Infants 3-11 months[2)]		Up to 2 g and 20 cm^2 for one hour[5)]
Toddlers and children 1-5 years		Up to 10 g and 100 cm^2 for 1-5 hours[6)]
Children 6-11 years		Up to 20 g and 200 cm^2 for 1-5 hours[6)]
Paediatric patients with atopic dermatitis	Prior to removal of mollusca	Application time: 30 minutes

[1)] In term newborn infants and infants below 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, see sections 4.4 and 4.8.
[2)] EMLA should not be used in infants up to 12 months of age receiving treatment with methaemoglobin-inducing agents, because of safety concerns, see sections 4.4 and 4.8.
[3)] EMLA should not be used at less than 37 weeks gestational age, because of safety concerns, see section 4.4.
[4)] Application for > 1hour has not been documented.
[5)] No clinically significant increase in methaemoglobin levels has been observed after an application time of up to 4 hours on 16 cm^2.

[6)] After longer application time anaesthesia decreases.

Safety and efficacy for the use of EMLA on genital skin and genital mucosa have not been established in children younger than 12 years.

Available paediatric data do not demonstrate adequate efficacy for circumcision.

Elderly
No dose reduction is necessary in elderly patients (see sections 5.1 and 5.2).

Hepatic impairment
A reduction of a single dose is not necessary in patients with impaired hepatic function (see section 5.2).

Renal impairment
A dose reduction is not necessary among patients with restricted renal function.

Method of administration

Cutaneous use

The protective membrane of the tube is perforated by applying the cap.
One gram of EMLA pressed out of a tube of 30 g is approximately 3.5 cm. If high levels of accuracy in dosing are required to prevent overdose (ie, at doses approaching the maximum in newborn infants or if two applications may be required in a 24 hour period), a syringe can be used where 1 mL = 1 g.

A thick layer of EMLA should be applied to the skin, including genital skin, under an occlusive dressing. For application to larger areas, such as split-skin grafting, an elastic bandage should be applied on top of the occlusive dressing to give an even distribution of cream and protect the area. In the presence of atopic dermatitis, the application time should be reduced.

For procedures related to genital mucosa, no occlusive dressing is required. The procedure should be commenced immediately after removal of the cream.

For procedures related to leg ulcers, a thick layer of EMLA should be applied under an occlusive dressing. Cleansing should start without delay after removal of the cream.

The EMLA tube is intended for single use when used on leg ulcers: The tube with any remaining contents should be discarded after each occasion that a patient has been treated.

4.3 Contraindications

Hypersensitivity to 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

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.

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

Due to the potentially enhanced absorption on the newly shaven skin, it is important to adhere to the recommended dosage, area and time of application (see section 4.2).

Care should be taken when applying EMLA 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 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 should not be applied to an impaired tympanic membrane. Tests on laboratory animals have shown that EMLA has an ototoxic effect when instilled into the middle ear. Animals with an intact tympanic membrane, however, show no abnormality when exposed to EMLA 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 immunization response, as assessed by local wheal formation, is not affected when EMLA is used prior to BCG vaccination, the results of intracutaneous injections of live vaccines should be monitored.

EMLA contains castor oil polyoxyl hydrogenated, which may cause skin reactions.

Paediatric population
Studies have been unable to demonstrate the efficacy of EMLA for heel lancing in newborn infants.

In newborn infants/infants younger than 3 months a transient, clinically insignificant increase in methaemoglobin levels is commonly observed up to 12 hours after an application of EMLA within the recommended dosing.
If the recommended dose is exceeded the patient should be monitored for system adverse reactions secondary to methaemoglobinaemia (see sections 4.2, 4.8 and 4.9).

EMLA should not be used
- in newborn infants/infants up to 12 months of age receiving concomitant treatment with methaemoglobin-inducing agents.
- in preterm newborn infants with a gestational age less than 37 weeks as they are at risk of developing increased methaemoglobin levels.

Safety and efficacy for the use of EMLA on genital skin and genital mucosa have not been established in children younger than 12 years.

Available paediatric data do not demonstrate adequate efficacy for circumcision.

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, nitrofuradantin, phenytoin, phenobarbital).This list is not exhaustive.

With large doses of EMLA, 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.

Paediatric population
Specific interaction studies in children have not been performed. Interactions are likely to be similar to the adult population.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although topical application is associated with only a low level of systemic absorption, the use of EMLA in pregnant women should be undertaken with care because insufficient data are available concerning the use of EMLA 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.

Breastfeeding
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 can be used during breastfeeding 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 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 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] Application site erythema[1, 2, 3] Application site oedema [1, 2, 3] Application site warmth [2, 3] Application site pallor [1, 2, 3]	Burning sensation[1] Application site irritation[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
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 (see Section 4.9), in newborn infants and infants aged 0 to 12 months.

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 listed in Appendix V.

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 susceptible individuals (section 4.4), with too frequent dosing in newborn infants and infants below 12 months of age (section 4.2) and in conjunction with methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofuradantin, 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: anesthetics, local; amides;
ATC code: N01B B20

Mechanism of action
EMLA 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 stabilize 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
EMLA is applied to intact skin under an occlusive dressing. The time needed to achieve reliable anaesthesia of intact skin is 1 to 2 hours, depending on the type of procedure. The local anaesthetic effect improves with longer application times from 1 to 2 hours in most parts of the body, with the exception of the skin of the face and the male genitals. Because of thin facial skin and high tissue blood flow, maximal local anaesthetic effect is obtained after 30-60 minutes on the forehead and on the cheeks. Similarly, local anaesthesia of the male genitals is achieved after 15 minutes. The duration of anaesthesia following the application of EMLA for 1 to 2 hours is at least 2 hours after removal of the dressing, except in the face

where the duration is shorter. EMLA is equally effective and has the same anaesthetic onset time across the range of light to dark pigmented skin (skin types I to VI).

In clinical studies of EMLA on intact skin, no differences in safety or efficacy (including anaesthetic onset time) were observed between geriatric patients (aged 65 to 96 years) and younger patients.

EMLA produces a biphasic vascular response involving initial vasoconstriction followed by vasodilatation at the application site (see section 4.8). Irrespective of the vascular response, EMLA facilitates the needle procedure compared to placebo cream. 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). EMLA may cause a transient increase in skin thickness, partly caused by hydration of the skin under the occlusive dressing. The skin thickness decreases over the course of 15 minutes air exposure.

The depth of cutaneous anaesthesia increases with application time. In 90% of patients the anaesthesia is sufficient for the insertion of a biopsy punch (4 mm diameter) to a depth of 2 mm after 60 minutes and 3 mm after 120 minutes EMLA treatment.

The use of EMLA prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines does 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.

Genital mucosa

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

After a 5-10 minute application of EMLA to female genital mucosa the average duration of effective analgesia to an argon laser stimulus, which produced a sharp, pricking pain was 15-20 minutes (individual variations in the range 5-45 minutes).

Leg ulcers

Reliable anaesthesia for the cleansing of leg ulcers is achieved after an application time of 30 minutes in most patients. An application time of 60 minutes may improve the anaesthesia further. The cleansing procedure should start within 10 minutes of removal of the cream. Clinical data from a longer waiting period are not available. EMLA reduces the postoperative pain for up to 4 hours after debridement. EMLA reduces the number of cleansing sessions required to achieve a clean ulcer compared to debridement with placebo cream. No negative effects on ulcer healing or bacterial flora have been observed.

Paediatric population

Clinical studies involved more than 2,300 paediatric patients of all age groups and demonstrated efficacy for needle pain (venipuncture, cannulation, sc and im vaccinations, lumbar puncture), laser treatment of vascular lesions, and curettage of molluscum contagiousum. EMLA diminished the pain of both needle insertion and injection of vaccines. Analgesic efficacy increased from 15 to 90 minutes application on normal skin but on vascular lesions 90 minutes provided no benefit over 60 min. There was no benefit of EMLA versus placebo for liquid nitrogen cryotherapy of common warts No adequate efficacy for circumcision could be demonstrated.

Eleven clinical studies in newborn infants 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.

The use of EMLA prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-Haemophilus influenzae b or Hepatitis B vaccines 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

Absorption, distribution, biotransformation and elimination

The systemic absorption of lidocaine and prilocaine from EMLA is dependent upon the dose, area of application and application time. Additional factors include thickness of the skin (which varies in different areas of the body), other conditions such as skin diseases, and shaving. Following application to leg ulcers, the characteristics of the ulcers may also affect the absorption. Plasma concentrations after treatment with EMLA are 20-60% lower for prilocaine than for lidocaine, because of a larger volume of distribution and more rapid clearance. The major elimination pathway of lidocaine and prilocaine is via hepatic metabolism and metabolites are renally excreted. However, the rate of metabolism and elimination of the local anaesthetics after topical application of EMLA are governed by the rate of absorption. Therefore, a decrease in clearance, such as in patients with severely impaired liver function, has limited effects on the systemic plasma concentrations after a single dose of EMLA, and after single doses repeated once daily short term (up to 10 days).

Symptoms of local anaesthetic toxicity become increasingly apparent at increasing plasma concentration from 5 to 10 µg/mL of either active substance. It should be assumed that the toxicity of lidocaine and prilocaine are additive.

Intact skin

Following 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 application.

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

In studies of split-skin grafting in adults application for up to 7hours 40 minutes to the thigh or upper arm to an area of up to 1,500 cm^2 resulted in maximum plasma concentrations not exceeding 1.1 µg/mL lidocaine and 0.2 µg/mL prilocaine.

Genital mucosa

After the application of 10 g EMLA 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.

Leg ulcer

Following a single application of 5 to 10 g of EMLA to leg ulcers with an area of up to 64 cm^2 for 30 minutes, the maximum plasma concentrations of lidocaine (range 0.05-0.25 µg/mL, one individual value of 0.84 µg/mL) and of prilocaine (0.02-0.08 µg/mL) were reached within 1 to 2.5 hours.

After an application time of 24 hours to leg ulcers with an area of up to 50-100 cm^2, the maximum plasma concentrations of lidocaine (0.19-0.71 µg/mL) and of prilocaine (0.06-0.28 µg/mL) were usually reached within 2 to 4 hours.

Following repeated application of 2-10 g EMLA to leg ulcers with an area of up to 62 cm^2 for 30-60 minutes 3-7 times a week for up to 15 doses during a period of one month, there was no apparent accumulation in plasma of lidocaine and its metabolites monoglycinexylidide and 2,6-xylidine or of prilocaine and its metabolite ortho-toluidine. The maximum observed plasma concentration for lidocaine, monoglycinexylidide and 2,6-xylidine were 0.41, 0.03 and 0.01 µg/mL respectively. The maximum observed plasma concentrations for prilocaine and ortho-toluidine were 0.08 µg/mL and 0.01 µg/mL respectively.

Following repeated application of 10 g EMLA to chronic leg ulcers with an area between 62-160 cm^2 for 60 minutes once daily during 10 consecutive days, the mean maximum plasma concentration of the sum of lidocaine and prilocaine concentrations was 0.6 µg/mL. The maximum concentration does not depend on the patient´s age but is significantly ($p<0.01$) related to the size of the ulcer area. Increasing the ulcer area by 1 cm^2 results in an increased C_{max} for the sum of lidocaine and prilocaine concentrations of 7.2 ng/mL. The sum of the maximum plasma concentrations of lidocaine and prilocaine is less than one-third of those associated with toxic reactions, with no apparent accumulation over 10 days.

Special populations
Elderly patients
Plasma concentrations of lidocaine and prilocaine in both geriatric and non-geriatric patients following application of EMLA to intact skin are very low and well below potentially toxic levels.

Paediatric population
The maximum plasma concentrations of lidocaine and prilocaine after application of EMLA in paediatric patients of different ages were also below potentially toxic levels. See table 4.

Table 4. Plasma concentrations of lidocaine and prilocaine in paediatric age groups from 0 months to 8 years of age

Age	Applied amount of cream	Application time of the cream on the skin	Plasma concentration [ng/ml]	
			Lidocaine	Prilocaine
0 - 3 months	1 g/10 cm^2	1 hour	135	107
3 - 12 months	2 g/16 cm^2	4 hours	155	131
2 - 3 years	10 g/100 cm^2	2 hours	315	215
6 - 8 years	10 - 16 g/100-160 cm^2 (1 g/ 10 cm^2)	2 hours	299	110

5.3 Preclinical safety data

In animal studies the toxicity noted after high doses of either lidocaine or prilocaine, alone or in combination, consisted of effects on the central nervous and cardiovascular systems. When lidocaine and prilocaine were combined, only additive effects were seen, with no indication of synergism or unexpected toxicity. Both active substances were shown to have a low oral acute toxicity, providing a good safety margin in the event that EMLA is inadvertently swallowed. In studies on reproduction toxicity, embryotoxic or fetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit and for prilocaine starting at doses of 100 mg/kg i.m. in the rat. At doses below the maternal toxic range in the rat, lidocaine has no effect on the postnatal development of the offspring. An impairment of the fertility of male or female rats by lidocaine or prilocaine was not observed. Lidocaine crosses the placental barrier by means of simple diffusion. The ratio of the embryofetal dose to the maternal serum concentration is 0.4 to 1.3.

Neither local anaesthetic showed a genotoxic potential in either in vitro or in vivo genotoxicity tests. Cancer studies have not been performed with either lidocaine or prilocaine alone or in combination, due to the indication and duration of therapeutic use of these active substances.

A metabolite of lidocaine, 2,6-dimethylaniline, and a metabolite of prilocaine, σ-toluidine, showed evidence of genotoxic activity. These metabolites have been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. Risk assessments comparing the calculated maximum human exposure from intermittent use of lidocaine and prilocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

Local tolerance studies using a 1:1 (w/w) mixture of lidocaine and prilocaine as an emulsion, cream or gel indicated that these formulations are well tolerated by intact and damaged skin and mucosal membranes.

A marked irritative reaction was seen after single ocular administration of a 50 mg/g lidocaine + prilocaine 1:1 (w/w) emulsion, in an animal study. This is the same concentration of local anaesthetics and a similar formulation as for EMLA. This ocular reaction may have been influenced by the high pH of the formulation of the emulsion (approximately 9), but is probably also partly a result of the irritative potential of the local anaesthetics themselves.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

Not all pack sizes may be marketed.

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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

EMLA and associated names (see Annex I) 25mg/g + 25mg/g cream
[See Annex I - To be completed nationally]
lidocaine / prilocaine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Cutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid contact with eyes.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Aluminum Tube 5 g

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

EMLA and associated names (see Annex I) 25mg/g + 25mg/g cream
[See Annex I - To be completed nationally]
lidocaine / prilocaine

Cutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 g

6. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

Aluminum Tube -30 g

1. NAME OF THE MEDICINAL PRODUCT

EMLA and associated names (see Annex I) 25mg/g + 25mg/g cream
[See Annex I - To be completed nationally]
lidocaine / prilocaine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

30 g cream

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Cutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid contact with eyes.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET

Package leaflet: Information for the user

EMLA and associated names (see Annex I) 25mg/g + 25mg/g cream
[See Annex I - To be completed nationally]

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EMLA is and what it is used for

EMLA contains two active substances called lidocaine and prilocaine. These belong to a group of medicines called local anaesthetics.

EMLA works by numbing the surface of the skin for a short time. It is put on the skin before certain medical procedures. This helps to stop pain on the skin; however you may still have the feelings of pressure and touch.

Adults, Adolescents and Children
It can be used to numb the skin before:

- Having a needle put in (for example, if you are having an injection or a blood test).
- Minor skin operations.

Adults and Adolescents
It can also be used:

- To numb the genitals before:
  - Having an injection.
  - Medical procedures such as removal of warts.

  A doctor or nurse should supervise the use of EMLA on the genitals.

Adults
It can also be used to numb the skin before:

- Cleansing or removal of damaged skin of leg ulcers

2. What you need to know before you use EMLA

Do not use EMLA

- if you are allergic to lidocaine or prilocaine, other similar local anaesthetics or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using EMLA
- if you or your child have a rare inherited illness that affects the blood called 'glucose-6-phosphate dehydrogenase deficiency'.
- if you or your child have a problem with blood pigment levels called 'methaemoglobinaemia'.
- Do not use EMLA on areas with skin rash, cuts, grazes or other open wounds, with the exception of a leg ulcer. If any of these problems are present, check with your doctor or pharmacist before using the cream.
- if you or your child have an itchy skin condition called 'atopic dermatitis', a shorter application time may be sufficient. Application times of longer than 30 minutes may result in an increased incidence of local skin reaction (see also section 4 "Possible side effects").
- if you take particular medicines for heart rhythm disorders (class III antiarrhythmics, such as amiodarone). In that case the doctor will monitor your heart function.

Due to the potentially enhanced absorption on the newly shaven skin, it is important to follow the recommended dosage, skin area and application time.

Avoid getting EMLA in the eyes, as it may cause irritation. If you accidentally get EMLA in your eye, you should immediately rinse it well with lukewarm water or salt (sodium chloride) solution. Be careful to avoid getting anything in your eye until feeling returns.

EMLA should not be applied to an impaired eardrum.

When you use EMLA before being vaccinated with live vaccines (e.g. tuberculosis vaccine), you should return to your doctor or nurse after the time period requested to follow-up the vaccination result.

Children and adolescents
In infants/newborn infants younger than 3 months a transient, clinically not relevant increase in blood pigment levels "methaemoglobinaemia" is commonly observed up to 12 hours after EMLA is put on.

The effectiveness of EMLA when drawing blood from the heel of newborn infants or to provide adequate analgesia for circumcision could not be confirmed in clinical studies.

EMLA should not be applied to the genital mucosa (e.g. in the vagina) of children (below 12 years of age) owing to insufficient data on absorption of active substances.

EMLA should not be used in children younger than 12 months of age who are being treated at the same time with other medicines that affect blood pigment levels "methaemoglobinaemia" (e.g. sulphonamides**,** see also Section 2 Other medicines and EMLA).

EMLA should not be used in preterm newborn infants.

Other medicines and EMLA
Tell your doctor or pharmacist if you are using / taking, have recently used / taken or might use / take any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because EMLA can affect the way some medicines work and some medicines can have an effect on EMLA.
In particular, tell your doctor or pharmacist if you or your child have recently used or been given any of the following medicines:

- Medicines used to treat infections, called 'sulphonamides' and nitrofuradantin.

- Medicines used to treat epilepsy, called phenytoin and phenobarbital.
- Other local anaesthetics.
- Medicines to treat an uneven heartbeat, such as amiodarone.
- Cimetidine or beta-blockers, which may cause an increase in the blood levels of lidocaine. This interaction is of no clinical relevance in short-term treatment with EMLA in recommended doses.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Occasional use of EMLA during pregnancy is unlikely to have any adverse effects on the foetus.

The active substances in EMLA (lidocaine and prilocaine) are excreted into breast milk. However, the amount is so small that there is generally no risk to the child.

Animal studies have shown no impairment of male or female fertility.

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

EMLA contains castor oil polyoxyl hydrogenated
Castor oil polyoxyl hydrogenated may cause skin reactions.

3. How to use EMLA

Always use EMLA exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Using EMLA
- Where to put the cream, how much to use and how long to leave it on for will depend on what it is needed for.
- Your doctor, pharmacist or nurse will put the cream on or show you how to do it yourself.
- When EMLA is used on the genitals, a doctor or nurse should supervise its use.

Do not use EMLA on the following areas:
- Cuts, grazes or wounds, excluding leg ulcers.
- Where there is a skin rash or eczema.
- In or near the eyes.
- Inside the nose, ear or mouth.
- In the back passage (anus).
- On the genitals of children.

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

The protective membrane of the tube is perforated by applying the cap.

Use on the skin before small procedures (such as having a needle put in or minor skin operations):

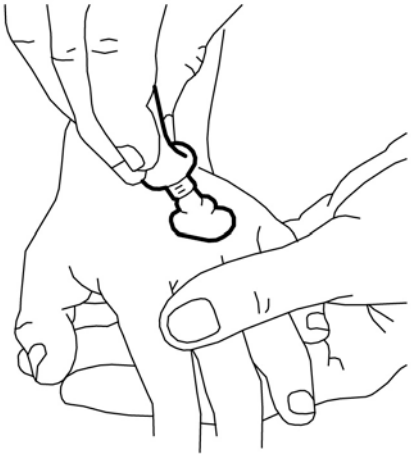
- The cream is put on to the skin in a thick layer. Your doctor, pharmacist or nurse will tell you where to put it.
- The cream is then covered by a dressing [plastic wrap]. This is taken off just before the procedure starts. If you are applying the cream yourself, make sure that you have been given dressings by

your doctor, pharmacist or nurse.

- The usual dose for adults and adolescents over 12 years is 2 g (grams).
- For adults and adolescents over 12 years put the cream on at least 60 minutes before the procedure (unless the cream is being used on the genitals). However, do not put it on more than 5 hours before.
- For children the amount of EMLA used and how long depends on their age. Your doctor, nurse or pharmacist will tell you how much to use and when it should be applied.

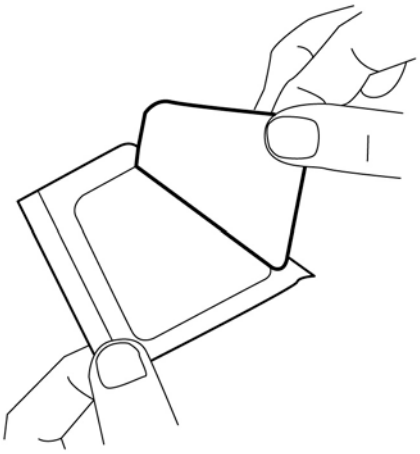
When you apply the cream, it is very important to exactly follow the instructions below:

1. Squeeze the cream into a mound where it is needed on your skin (for example where the needle is going to be put in). A line of cream of about 3.5 cm from the 30 g tube is equal to 1 g of cream. Half a 5 g tube corresponds to about 2 g EMLA.



2. Do not rub the cream in.

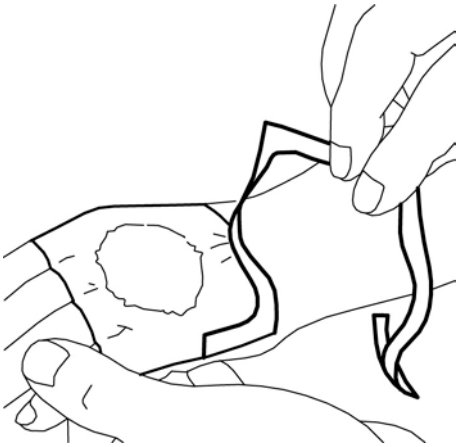
3. Peel the ‘centre cut-out’ from the dressing.



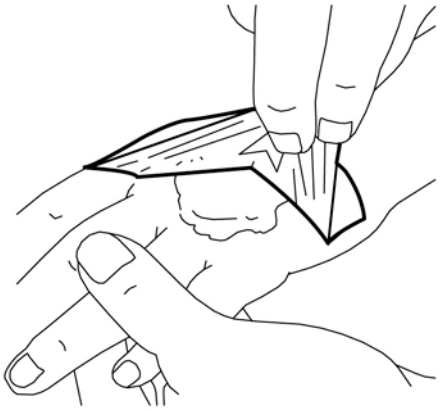
4. Peel the paper layer from the dressing.

5. Remove the covers of the dressing. Then place the dressing carefully over the mound of cream. Do not spread the cream under the dressing.

6. Remove the plastic backing. Smooth down the edges of the dressing carefully. Then leave it in place for at least 60 minutes.



7. Your doctor or nurse will take the dressing off and remove the cream just before they do the medical procedure (for example just before the needle is put in).



Use on larger areas of newly shaven skin before outpatient procedures (such as hair removal techniques):
The usual dose is 1 g of cream for each area of skin that is 10 cm² (10 square centimetres) in size, applied for 1 to 5 hours under a dressing. EMLA should not be used on an area of newly shaven skin larger than 600 cm² (600 square centimetres, e.g. 30 cm by 20 cm) in size. The maximum dose is 60 g.

Use on the skin before hospital procedures (such as split-skin grafting) that require deeper skin anaesthesia:
- EMLA can be used in this way on adults and adolescents over 12 years.
- The usual dose is 1.5 g to 2 g of cream for each of area of skin that is 10 cm^2 (10 square centimetres) in size.
- The cream is put on under a dressing for 2 to 5 hours.

Use on the skin prior to removal of wart-like spots called "mollusca"
- EMLA can be used on children and adolescents with a skin condition called "atopic dermatitis".
- The usual dose depends on the child's age and is used for 30 to 60 minutes (30 minutes if the patient has atopic dermatitis). Your doctor, nurse or pharmacist will tell you how much cream to use.

Use on genital skin before injections of local anaesthetics
- EMLA can be used in this way on adults and adolescents over 12 years only.
- The usual dose is 1 g of cream (1g to 2 g for female genital skin) for each area of skin that is 10 cm^2 (10 square centimetres) in size.
- The cream is put on under a dressing. This is done for 15 minutes on male genital skin and for 60 minutes on female genital skin.

Use on the genitals before minor skin surgery (such as removal of warts)
- EMLA can be used in this way on adults and adolescents over 12 years only.
- The usual dose is 5 g to 10 g of cream for 10 minutes. A dressing is not used. The medical procedure should then start straight away.

Use on leg ulcers before cleaning or removal of damaged skin
- The usual dose is 1g to 2 g of cream for each area of skin that is 10 cm^2 up to a total of 10 g.
- The cream is put on under an airtight dressing such as plastic wrap. This is done for 30 to 60 minutes before the ulcer is to be cleansed. Remove the cream with cotton gauze and start cleansing without delay.
- EMLA can be used before cleansing of leg ulcers for up to 15 times over a period of 1-2 months.
- The EMLA tube is intended for single use when used on leg ulcers: The tube with any remaining contents should be discarded after each occasion that a patient has been treated.

If you use more EMLA than you should
If you use more EMLA than your doctor, pharmacist or nurse has told you to, talk to one of them straight away, even if you do not feel any symptoms.

Symptoms of using too much EMLA are listed below. These symptoms are unlikely to happen if EMLA is used as recommended.
- Feeling light-headed or dizzy.
- Tingling of the skin around the mouth and numbness of the tongue.
- Abnormal taste.
- Blurred vision.
- Ringing in the ears.
- There is also a risk of 'acute methaemoglobinaemia' (a problem with blood pigment levels). This is more likely when certain medicines have been taken at the same time. If this happens, the skin becomes bluish-grey due to a lack of oxygen.

In serious cases of overdose, symptoms may include fits, low blood pressure, slowed breathing, stopped breathing and altered heartbeat. These effects may be life threatening.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Contact your doctor or pharmacist if any of the following side effects bother you or do not seem to go away. Tell your doctor about anything else that makes you feel unwell while you are using EMLA.

A mild reaction (paleness or redness of the skin, slight puffiness, initial burning or itching) may occur on the area on which EMLA is used. These are normal reactions to the cream and the anaesthetics and will disappear in a short while without any measures being needed.

If you experience any troublesome or unusual effects while you are using EMLA, stop using it and check with your doctor or pharmacist as soon as possible.

Common (may affect up to 1 in 10 people)
- Transient local skin reactions (paleness, redness, swelling) in the treated area during treatment of skin, genital mucosa or leg ulcers.
- An initially mild sensation of burning, itching or warmth at the treated area during treatment of genital mucosa or leg ulcers.

Uncommon (may affect up to 1 in 100 people)
- An initially mild sensation of burning, itching or warmth at the treated area during treatment of the skin.
- Numbness (tingling) in the treated area during treatment of the genital mucosa
- Irritation of the treated skin during treatment of leg ulcers.

Rare (may affect up to 1 in 1,000 people*)*
- Allergic reactions, which in rare cases may develop into anaphylactic shock (skin rash, swelling, fever, respiratory difficulties and fainting) during treatment of skin, genital mucosa or leg ulcers.
- Methaemoglobinaemia (blood disorder) during treatment of the skin.
- Small dot-shaped bleeding on the treated area (particularly on children with eczema after longer application times) during treatment of the skin.
- Irritation of the eyes if EMLA accidentally comes into contact with them during treatment of the skin.

Additional side effects in children
Methaemoglobinaemia, a blood disorder, which is more frequently observed, often in connection with overdose in newborn infants and infants aged 0 to 12 months.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EMLA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package and tube after "EXP:". The expiry date refers to the last day of that month.

[To be completed nationally]

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EMLA contains

- The active substances are: lidocaine and prilocaine

[To be completed nationally]

What EMLA looks like and contents of the pack

[To be completed nationally]

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Emla 5% - Crème
Belgium	Emla 25mg/25mg crème
Cyprus	Emla Cream 5%
Czech Republic	Emla krém 5%
Denmark	Emla
Finland	EMLA
France	EMLA 5 POUR CENT, crème

Germany	EMLA
Greece	EMLA
Iceland	Emla
Ireland	EMLA 5% w/w Cream
Italy	EMLA
Latvia	Emla 5 % cream
Luxembourg	Emla 25mg/25mg crème
Malta	EMLA 5% w/w Cream
Norway	Emla
Poland	EMLA
Portugal	Emla
Spain	EMLA 25 mg/g + 25 mg/g crema
Sweden	EMLA
The Netherland	Emla
United Kingdom	Emla Cream 5%

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

[To be completed nationally]