PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

EMLA® Cream

Lidocaine and Prilocaine Cream

Cream, 2.5% Lidocaine and 2.5% Prilocaine, Topical

Manufacturer's Standard

EMLA® Patch

Lidocaine and Prilocaine Transdermal Patch

Transdermal Patch, 2.5% Lidocaine and 2.5% Prilocaine, Topical

Topical Anesthetic for Dermal Analgesia

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations	04/2022
7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women	04/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EMLA should only be used for the approved indications because maximum safe doses for other uses are not known. Serious and life-threatening adverse events have occurred when EMLA cream was applied to large areas of skin for topical analgesia during cosmetic procedures (e.g., laser depilation) (see 7 WARNINGS AND PRECAUTIONS**; 8** ADVERSE REACTIONS**).**

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is indicated for:

- Topical analgesia of **intact skin** in connection with
    - needle insertion, e.g., i.v. catheters or prior to blood sampling
- vaccination with only the following vaccines, shown not to interact with EMLA in clinical trials: MMR, DPTP; *Haemophilus influenzae* b and Hepatitis B (see 14 CLINICAL TRIALS, Topical Analgesia in Pediatrics , Vaccination
    -). Since the effect of EMLA on the immune response to any other vaccine is unknown, it cannot be recommended for use with other vaccines.
    - superficial surgical procedures, e.g., removal of molluscum contagiosum, split skin grafting, electrolysis
    - laser treatment for superficial skin surgeries, such as treatment of telangiectasia, port wine stains, warts, moles, skin nodules, and scar tissue
- Topical analgesia of **genital mucosa** in connection with
    - local infiltration anesthesia
    - surgical procedures lasting not longer than 10 minutes on small superficial localized lesions, e.g., removal of condylomata by laser or cautery, and biopsies
- Topical analgesia of **leg ulcers** in connection with
    - mechanical/sharp cleansing/debridement, e.g., the removal of necrotic tissue and debris by curettes, scissors, tweezers, etc.

EMLA Patch (lidocaine 2.5% and prilocaine 2.5%) is indicated for use in:

- Topical analgesia of **intact skin** in connection with
    - needle insertion, e.g., i.v. catheters or prior to blood sampling

- vaccination with only the following vaccines that have been shown not to interact with EMLA in clinical trials: MMR, DPTP; *Haemophilus influenzae* b and Hepatitis B (see 14 CLINICAL TRIALS, Topical Analgesia in Pediatrics , Vaccination
- Since the effect of EMLA on the immune response to any other vaccine is unknown, it cannot be recommended for use with other vaccines.

1.1 Pediatrics (<18 years of age):

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of EMLA in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. (see 14 CLINICAL TRIALS; 4 DOSAGE AND ADMINISTRATION; 7.1.3 Special Populations, Pediatrics).

EMLA is contraindicated for use in preterm infants (defined as gestational age less than 37 weeks) (see 2 CONTRAINDICATIONS).

1.2 Geriatrics:

Evidence from clinical studies and experience suggests that use in the geriatric population may be associated with differences in safety or effectiveness. There are insufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA (see 7.1.4 Special Populations, Geriatrics).

2 CONTRAINDICATIONS

EMLA (lidocaine and prilocaine) is contraindicated in:

- Patients who are hypersensitive to local anesthetics of the amide type or to any ingredients in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Patients with congenital or idiopathic methaemoglobinaemia

- Procedures requiring large amounts of EMLA over a large body area that are not conducted in a facility where the healthcare professionals are trained in the diagnosis and management of dose-related toxicity and other acute emergencies that may arise and, the appropriate resuscitative treatments and equipment required for management of toxic reactions and related emergencies are available

- Infants who require treatment with methemoglobin-inducing agents, e.g., sulfonamides and are 12 months of age or younger (see 9 DRUG INTERACTIONS)

- Preterm infants (defined as gestational age less than 37 weeks)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- EMLA should only be used for approved indications because maximum safe doses for other uses are not known.

- Serious and life-threatening adverse events have occurred when EMLA cream was applied to large areas of skin for topical analgesia during cosmetic procedures (e.g., laser depilation) (see 2 CONTRAINDICATIONS; 8 ADVERSE REACTIONS; 5 OVERDOSAGE).

- At each recommended dose (g cream / cm^2 skin area), the depth and effectiveness of analgesia are dependant upon the total time elapsed between application and procedure (i.e., total time is a combination of the period of cream application and the period following the removal of the cream up until the procedure is performed).

- EMLA Cream should only be applied to intact, unbroken skin, with the exception for leg ulcers.

4.2 Recommended Dose and Dosage Adjustment

Table 1 and Table 2 detail dosing recommendations for EMLA cream, for adults and pediatrics, respectively, while Table 3 provides common references for the size of each specific recommended maximum skin area.

Table 4 and Table 5 detail dosing recommendations for EMLA patch, for adults and pediatrics respectively.

Do not exceed dosages outlined in the tables below.

EMLA Cream

Table 1 ADULTS: Recommended Dosage of EMLA Cream According to Body Surface, and Procedure[a]

Surface	Procedure	Cream Application
Intact Skin	Minor procedures, e.g., needle insertion, surgical treatment of localized lesions, and laser treatment[a, b].	Apply a thick layer of cream under an occlusive dressing to selected area(s). Remove the dressing and clean the area of any excess cream thoroughly prior to the procedure. In general, approx. 1.5 g/10 cm^2.

Surface	Procedure	Cream Application
		Approx. 2 g (1/2 of 5 g tube) for a minimum of 1 hour. Maximum 5-hour application[c].
	Dermal procedures performed on larger areas, in a hospital setting, e.g., split-skin grafting[d].	1.5 - 2 g/10 cm^2, up to a total of 60 g. Maximum recommended treated area: 400 cm^2[(d)]. Minimum application time: 2 hours. Maximum application time: 5 hours[c].
Genital Mucosa	Surgical procedures lasting not longer than 10 minutes on localized lesions, e.g., removal of genital warts, and prior to local infiltration anesthesia.	Approx. 2 g (1/2 of 5 g tube) per lesion for 5-10 minutes. Maximum 10 g[e]. Occlusion is not necessary. Commence procedure immediately after removal of cream.
Leg Ulcers	Mechanical cleansing/debridement of leg ulcers[f]	Approx. 1-2 g/10cm^2 area, up to a total of 10 g. Cover with an occlusive dressing. Minimum 30 minutes application time, with up to 60 minutes for necrotic tissue with a thicker penetration barrier. Cleansing should start immediately after removal of the cream.

a EMLA should only be used for approved indications because maximum safe doses for other uses are not known. Serious and life threatening adverse events have occurred when EMLA cream was applied to large areas of skin for topical analgesia during cosmetic procedures (e.g. laser depilation).

b Topical analgesia with EMLA has been evaluated in clinical trials in which laser treatments were for superficial skin surgeries, such as treatment of telangiectasia, port wine stains, warts, moles, skin nodules, and scar tissue.

c There is no benefit to application times longer than 5 hours, as the analgesic effectiveness of the cream dissipates over time.

d In clinical trials evaluating the analgesic effects of EMLA during split skin grafting, EMLA was well tolerated when applied to treatment areas of approximately 50 to 400 cm^2 (n=232). A small number of patients in these clinical trials had EMLA applied to treatment areas > 400 cm^2 (n=8).

e Pharmacokinetic data for doses larger than 10 g are not available.

f In the treatment of leg ulcers, EMLA cream has been repeatedly applied (up to 15 times within a 1-2 month period, at intervals of 1 to 4 days), with no apparent loss of effect or increase in local reaction.

Table 2 PEDIATRICS: Maximum Recommended Dosage of EMLA Cream According to Age

Age	Cream Application
In general, approx. 1 g/10 cm^2 area for 1 hour under a dressing to minimize the potential for the child to accidentally spread the cream outside of the treatment area. Remove the dressing and clean the area of any excess cream thoroughly prior to the procedure.	
Neonates 0 up to 3 months or <5 kg [a, b] (minimal gestational age is 37 weeks)	0.5 to 1.0 g, and up to 10 cm^2 area for approximately 1 hour. Standard dose = 1.0 g. Maximum 1-hour application[c, d.] No more than one application site at a time. The safety of repeated dosing has not been established.

Age	Cream Application
Infants 3 up to 12 months [b] and > 5 kg	Up to 2 g and 20 cm^2 for approximately 1 hour[e]. Maximum 4-hour application.
Children 1-6 years and > 10 kg	Up to 10 g and 100 cm^2 for a minimum of 1 hour. Maximum 5-hour application[f].
Children 7-12 years and > 20 kg	Up to 20 g and 200 cm^2 for a minimum of 1 hour. Maximum 5-hour application[f]

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of EMLA Cream should be restricted to that which corresponds to the patient's weight.

a Infants less than 3 months of age are at higher risk of methaemoglobinaemia due to immature reductase enzyme pathways.

b Until further clinical data is available, EMLA should not be used in infants who require treatment with methemoglobin-inducing agents, i.e., sulfonamides, and are 12 months of age or younger.

c The safety of a longer application time has not been established.

d Of eight cases of neonates with > 5% methemoglobin, misuse was documented in seven (overdose, or concomitant methemoglobin-inducing meds).

e No clinically significant increase in methemoglobin fraction has been observed after an application time of up to 4 hours on 16 cm^2.

f There is no benefit to application times longer than 5 hours, as the analgesic effectiveness of the cream dissipates over time.

1 g of EMLA cream administered from the 30 g aluminium tube is equivalent to a ribbon of cream of approximately 3.5 cm (approximately 1.5 inches).

Table 3 Conversion of Maximum Recommended Skin Areas (cm^2) to $Inches^2$ and to a Reference Object of Comparable Size

cm^2	$inch^2$	Area Reference
10	approx. 2	A little larger than the size of a two dollar coin ("toonie").
16	approx. 3	A little larger than the size of a credit card.
100	approx. 4	A little larger than the size of two credit cards.
200	approx. 6	A little larger than the size of a standard postcard.

EMLA Patch

Table 4 ADULTS: Recommended Dosage of EMLA Patch

Surface	Procedure	Transdermal Patch Application
Intact Skin only	Minor procedures, e.g., needle insertion.	Apply patch(es) only to selected skin area(s) <10 cm^2. One or more patches applied for a minimum of 1 hour. Maximum 5-hour application[a] Remove patch and clean the area thoroughly prior to procedure.

a There is no benefit to application times longer than 5 hours, as the analgesic effectiveness of the cream in the patch dissipates over time.

Table 5 PEDIATRICS: Maximum Recommended Dosage of EMLA Patch by Age Group

Age	Transdermal Patch Application
	Apply patch(es) only to selected skin area(s) < 10 cm^2 [a] Remove patch and clean the area thoroughly prior to procedure.
Neonates 0 up to 3 months or <5 kg[b,c]	1 patch applied for approx. 1 hour. Maximum 1-hour application[d]. No more than 1 patch applied at the same time. The safety of repeated dosing has not been established.
Infants 3 up to 12 months[c] and > 5 kg	Patch applied for approx. 1 hour[d]. Maximum 4-hour application. No more than 2 patches applied at the same time[e].
Children 1-6 years and > 10 kg	One or more patches applied for a minimum of 1 hour. Maximum 5-hour application[f]. Maximum dose is 10 g (10 patches).
Children 7-12 years and > 20 kg	One or more patches applied for a minimum of 1 hour. Maximum 5-hour application[f]. Maximum dose is 20 g (20 patches).

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of EMLA Patch should be restricted to that which corresponds to the patient's weight.

a The size of the patch makes it less suitable for use on certain parts of the body in neonates and infants.

b Infants less than 3 months of age are at higher risk of methaemoglobinaemia due to immature reductase enzyme pathways.

c Until further clinical data is available, EMLA should not be used in infants who require treatment with methemoglobin-inducing agents, i.e., sulfonamides, and are 12 months of age or younger.

d The safety of a longer application time has not been established.

e No clinically significant increase in methemoglobin fraction has been observed after an application time of up to 4 hours on 16 cm^2.

f There is no benefit to application times longer than 5 hours, as the analgesic effectiveness of the cream in the patch dissipates over time.

Conditions where dosage adjustments may be required:

- In acutely ill, debilitated or elderly patients, those with impaired elimination, and patients with severe hepatic impairment who are more sensitive to systemic effects due to increased blood levels of lidocaine and prilocaine from repeated doses of EMLA (lidocaine and prilocaine), smaller application areas are recommended to avoid toxicity. Decreased duration of application is not recommended as this may decrease the analgesic effect.

- In patients who are administered other local anesthetics or amide type local anesthetics (see 9 DRUG INTERACTIONS).

In patients with atopic dermatitis, extra care should be taken when applying EMLA. A shorter application time is recommended (see 7 WARNINGS AND PRECAUTIONS, Skin and 10.3 Pharmacokinetics).

- Pediatrics:
    - Pediatric patients should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious adverse events (e.g., methaemoglobinaemia) (see 7.1.3 Special Populations, Pediatrics).
    - EMLA should not be used in infants who require treatment with methemoglobin-inducing agents, i.e., sulfonamides, and are 12 months of age or younger.
    - EMLA (lidocaine and prilocaine) is contraindicated in preterm infants (defined as gestational age less than 37 weeks) (see 2 CONTRAINDICATIONS).

4.4 Administration

Cream: A thick layer of cream should be applied to the skin, under an occlusive dressing.

Transdermal Patch: One or more patch(es) should be applied to the skin area(s) selected.

5 OVERDOSAGE

A few fatal cases have been reported with limited information and doses unknown, therefore a causal relationship to EMLA (lidocaine and prilocaine) could not be established.

Symptoms

General

Local anesthetic toxicity is manifested by symptoms of nervous system excitation and in severe cases, central nervous and cardiovascular depression.
In the unlikely event of toxicity following epidermal application of EMLA, signs of systemic toxicity anticipated would be similar in nature to those observed following other routes of administration of local anesthetics.

Methaemoglobinaemia

Rare cases of methaemoglobinaemia have been reported.

Mild methaemoglobinaemia is characterized by tissue cyanosis, a bluish-grey or brownish discoloration of the skin, especially around the lips and nail beds, which is not reversed by breathing 100% oxygen. Clinical signs may also include pallor and marbleization.

Severe methaemoglobinaemia (MetHb concentrations above approximately 25%) is associated with signs of hypoxemia, ie. dyspnea, tachycardia and depression of consciousness.

Drug-induced methaemoglobinaemia may occur with the use of drugs including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine.

Acetaminophen has been shown to induce methemoglobin formation *in vitro* and in animals. In humans, methemoglobin formation is very rare at therapeutic doses and overdoses of acetaminophen.

It should be kept in mind that EMLA is contraindicated for patients with congenital or idiopathic methaemoglobinaemia and for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs. Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methaemoglobinaemia (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS).

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.

Treatment
Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive drugs.

In neonates, methemoglobin concentrations of up to 5 - 6% are not considered to be of clinical significance, with treatment of symptomatic methaemoglobinaemia not typically necessary unless methemoglobin concentrations are above 25 - 30%. However, the severity of clinical symptoms should be the primary consideration in the decision to initiate treatment, rather than the level of methemoglobin. Most patients recovered spontaneously after removal of the cream.

Methaemoglobinaemia may be treated with a slow intravenous injection of methylene blue. It has been reported in published literature that methylene blue should be used cautiously as a treatment for methaemoglobinaemia in patients with glucose-6-phosphate dehydrogenase deficiency because it may not be effective for these patients and may cause hemolytic anemia (see 7 WARNINGS AND PRECAUTIONS).

There are anecdotal reports of patients consuming EMLA cream or patches; all cases resolved without serious injury. Such patients should be monitored for symptoms of systemic toxicity.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Cream, 2.5%/2.5%	carboxypolymethylene, polyoxyethylene hydrogenated castor oil, sodium hydroxide, purified water
Topical	Transdermal Patch, 2.5%/2.5%	cellulose and cotton disc, polyethylene foam with acrylate adhesive, polyamide/aluminium/plastic and polypropylene/aluminium/plastic laminates

Dosage Forms

The active ingredients in EMLA (lidocaine and prilocaine) in a 1:1 ratio, form a liquid eutectic mixture at temperatures above 16°C. EMLA is based on an emulsion system of this eutectic mixture and contains 2.5% lidocaine and 2.5% prilocaine. EMLA Cream and EMLA Patch differ in viscosity due to their different concentrations of carboxypolymethylene. EMLA contains no preservatives in view of the antimicrobial activity of lidocaine and prilocaine.

- **EMLA Cream** is available in 5 g aluminium tubes with occlusive dressings and 30 g aluminium tubes without dressings for use as a topical anesthetic for dermal analgesia.

  EMLA Cream Composition (1 g of EMLA)
  Medicinal Ingredients:
  Lidocaine 25 mg
  Prilocaine 25 mg

  Non-medicinal Ingredients:
  Carboxypolymethylene
  Polyoxyethylene hydrogenated castor oil
  Sodium hydroxide to adjust pH to 8.7-9.7
  Water, purified

- **EMLA Patch** is a single-dose unit in the form of an occlusive dressing. It is composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring. The disc contains 1 g of the EMLA emulsion, the active contact surface area being approximately 10 cm^2. The surface area of the entire patch is approximately 40 cm^2. EMLA Patch is available in boxes of 2 or 20 single-use transdermal patches per box, for use as a topical anesthetic for dermal analgesia.

EMLA Patch Composition (1 g of EMLA)
Medicinal Ingredients:
Lidocaine 25 mg
Prilocaine 25 mg

Non-medicinal Ingredients:
Carboxypolymethylene
Polyoxyethylene hydrogenated castor oil
Sodium hydroxide to adjust pH to 8.7-9.7
Water, purified

Transdermal Patch Components:
Cellulose and cotton disc
Natural rubber latex
Polyethylene foam with acrylate adhesive
Polyamide/aluminium/plastic and polypropylene/aluminium/plastic laminates

7 WARNINGS AND PRECAUTIONS

General

Serious and life-threatening systemic adverse events, including methaemoglobinaemia, central nervous system toxicity and cardiovascular collapse have occurred when EMLA cream was applied to large areas of skin for topical analgesia during cosmetic procedures (e.g., laser depilation) (see 8 ADVERSE REACTIONS; 5 OVERDOSAGE). EMLA should only be used for the approved indications because maximum safe doses for other uses are not known.

Patients should be instructed to strictly adhere to dosing recommendations and application time and to limit the dose and area of application (see 4 DOSAGE AND ADMINISTRATION).

When using EMLA in younger children, especially infants under the age of 3 months, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see 4 DOSAGE AND ADMINISTRATION; 7.1.3 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics). Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious adverse events (e.g., methaemoglobinaemia).

Repeated doses of EMLA (lidocaine and prilocaine) may increase blood levels of lidocaine and prilocaine. EMLA should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and prilocaine including acutely ill, debilitated, or elderly patients, and patients with severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION).

Due to insufficient data on absorption, EMLA should not be applied to open wounds as a result of trauma. Note: Leg ulcers often follow a slight trauma but are not classified as traumatic wounds.

Special care should also be employed to ensure the occlusive bandage or patch is secure. This will avoid accidental dislocation and exposure of EMLA, especially in young children.

EMLA is not recommended in any clinical situation where it can penetrate or migrate into the middle ear. Tests on laboratory animals (guinea pigs) have shown that EMLA has an ototoxic effect when instilled into the middle ear. When the same animals were exposed to EMLA in the external auditory canal, no abnormalities were seen. EMLA causes minor structural damage to the tympanic membrane in rats when applied directly to the membrane.

Carcinogenesis and Mutagenesis
The active substances in EMLA, lidocaine and prilocaine, have not been evaluated for carcinogenicity in animal studies following topical application; neither has EMLA the eutectic mixture of lidocaine and prilocaine bases. Metabolites of prilocaine have been shown to be carcinogenic after life-time, once-daily oral exposure in laboratory animals (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. However, a metabolite of lidocaine, 2,6-xylidine, showed weak evidence of activity in some genotoxicity tests (see 16 NON-CLINICAL TOXICOLOGY, Genotoxicity

Driving and Operating Machinery
Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

In cases of suspected methaemoglobinaemia, CO-oximetry may provide more accurate measurements of oxygen saturation than pulse oximeter values (see 5 OVERDOSAGE and 7.1.3 Pediatrics).

Hepatic/Biliary/Pancreatic
Because amide-type local anesthetics are metabolized by the liver, these drugs, especially repeated doses, should be used cautiously in patients with hepatic disease. For patients with severe hepatic disease, a reduced capacity to metabolize local anesthetics may increase the risk of developing toxic plasma concentrations (see 4 DOSAGE AND ADMINISTRATION).

Immune

Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur. They are characterized by urticaria, angioedema, bronchospasm, or in the most severe instances, anaphylactic shock. If these reactions occur they should be managed according to standard clinical practice.

Vaccination: Efficacy of immunization with live vaccines may be affected, as lidocaine and prilocaine have been shown to inhibit viral and bacterial growth. The effect of EMLA on intradermal injections of live vaccines has not been determined.

Ophthalmologic

EMLA should not be applied to, or near to, the eyes as it causes corneal irritation if it comes into contact with the cornea. This reaction may be reversible. In addition, the loss of protective reflexes may allow corneal irritation and potential abrasion. Take care to avoid accidental contact of EMLA with the eyes (e.g., rubbing the eyes after using fingers to apply EMLA elsewhere), as the analgesic effect may result in damage from undetected foreign bodies. If eye contact does occur, immediately rinse the eye in water or sodium chloride solution and protect the eye until sensation returns.

Renal

In individuals with normal renal function, the extent of systemic absorption of lidocaine and prilocaine is low, 5-14% after cutaneous application, higher on genital mucosa and leg ulcer. Only a small fraction of lidocaine and prilocaine (2-5%) is excreted unchanged in the urine, as the primary metabolism occurs in the liver (see 10.3 Pharmacokinetics). The pharmacokinetics of lidocaine and its main metabolite were not altered significantly in haemodialysis patients (n=4) who received an intravenous dose of lidocaine. Therefore, renal impairment is not expected to significantly affect the pharmacokinetics of lidocaine and prilocaine, when EMLA is used according to dosage instructions (see 4 DOSAGE AND ADMINISTRATION).

Skin

Care should be taken when applying EMLA to patients with atopic dermatitis. A more rapid and greater absorption through the skin is observed in these patients. Post marketing data and limited efficacy and safety data from studies that included a small number of pediatric patients with atopic dermatitis undergoing curettage of molluscum contagiosum indicate that caution is warranted when applying EMLA cream to patients with atopic dermatitis and a shorter application time should be used (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions
Atopic Dermatitis

There have been several case reports of purpuric reactions from post-marketing use of EMLA in pediatric patients. In most cases, children have had ongoing molluscum contagiosum and/or atopic constitution/dermatitis and an application time ≥30 minutes.

7.1 Special Populations

EMLA is contraindicated for patients with congenital or idiopathic methaemoglobinaemia and for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs (see 2 CONTRAINDICATIONS).

Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methaemoglobinaemia. In glucose-6-phosphate dehydrogenase deficient patients, the antidote methylene blue is ineffective at methaemoglobin reduction and is capable of oxidizing haemoglobin itself and, therefore, should not be given.

Patients who are acutely ill, debilitated or elderly, and patients with severe hepatic impairment may require dosing adjustments commensurate with age, weight and physical condition, because they may be more sensitive to systemic effects due to increased blood levels of lidocaine and prilocaine following repeated doses of EMLA (see 4 DOSAGE AND ADMINISTRATION).

7.1.1 Pregnant Women

Pregnancy

The safety of EMLA during pregnancy has not been established in humans.

Lidocaine and prilocaine cross the placental barrier and may be absorbed by the fetal tissues. It is reasonable to assume that lidocaine and prilocaine have been used in a large number of pregnant women and women of child-bearing 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 fetus. However, care should be given during early pregnancy when maximum organogenesis takes place.

Although, animal studies do not indicate any direct or indirect negative effects on pregnancy, parturition or postnatal development at clinically relevant doses, embryofoetal toxicity has been shown with subcutaneous/intramuscular administration of high doses of lidocaine or prilocaine much exceeding the exposure from topical application (see 16 NON-CLINICAL TOXICOLOGY).

Labor and Delivery

Should EMLA be used concomitantly with other products containing lidocaine and/or priolocaine during labor and delivery, the total dose contributed by all formulations should be considered.

7.1.2 Breast-feeding

Lidocaine and, in all probability, prilocaine, are excreted in human milk, but in such small quantities that there is generally no risk of the infant being affected at therapeutic dose levels due to low systemic absorption. EMLA can be used during breast-feeding, if clinically needed. If EMLA is used during breast-feeding, it should be applied away from the breast to prevent accidental ingestion.

7.1.3 Pediatrics

Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious adverse events (e.g., methaemoglobinaemia).

Methemoglobin (MetHb) concentrations are normally maintained below 2% of total hemoglobin, due to the activity of NADH-dehydrogenase which reduces metHb to hemoglobin. In neonates, NADH-dehydrogenase activity is not yet fully developed, and therefore metHb can accumulate, causing methaemoglobinaemia, a condition in which hemoglobin cannot bind and deliver oxygen normally.

A metabolite of prilocaine, o-toluidine, is known to induce methaemoglobinaemia. Therefore, in the neonate, in addition to ensuring that EMLA dosage recommendations result in safe lidocaine and prilocaine plasma concentrations, there is the additional need to ensure that o- toluidine-induced methaemoglobinaemia does not occur.

In neonates, increases in metHb concentrations of up to 5-6% are generally considered to be of little clinical significance, and treatment of symptomatic methaemoglobinaemia is typically not needed unless metHb concentrations are nearing 25%. (see 5 OVERDOSAGE)

When using EMLA in younger children, especially infants under the age of 3 months, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see 4 DOSAGE AND ADMINISTRATION).

In neonates (minimum gestation age: 37 weeks) and children weighing less than 20 kg, the area and duration of application should be limited (see 4 DOSAGE AND ADMINISTRATION, Table 2).

Studies have not demonstrated the efficacy of EMLA for heel lancing in neonates.
EMLA should not be applied to the genital mucosa of children or infants due to insufficient data on absorption.

In infants below the age of 3 months, the capacity of the MetHb reductase is lower than in older children and in adults. A transient, clinically insignificant increase in methemoglobin fraction is commonly observed up to 12 hours after an application of EMLA.

EMLA should not be used:

- in preterm infants (defined as a gestational age less than 37 weeks)
- in patients with congenital or idiopathic methaemoglobinaemia
- in infants who require treatment with methemoglobin-inducing agents such as sulfonamides, and are 12 months of age or younger (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS; 9 DRUG INTERACTIONS; 8 ADVERSE REACTIONS; 14 CLINICAL TRIALS)

Parents should be reminded of the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

7.1.4 Geriatrics

Elderly patients may require dosing adjustments (see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Greater sensitivity of some older individuals cannot be ruled out. There are insufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA.

During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours).

No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients. (see 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions in association with the use of EMLA (lidocaine and prilocaine) were local reactions such as paleness, erythema (redness) and edema. Other adverse experiences reported rarely include anaphylactic shock.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The adverse drug reactions included below for EMLA (lidocaine and prilocaine) represent data from both clinical and post-marketing experience.

	Adverse Reactions
Intact Skin (for all age groups)	
Common Events (>1%)	At the application site: transient local reactions such as paleness, erythema (redness) and edema.
Uncommon Events (>0.1% and <1%)	At the application site: skin sensations, e.g., an initial mild burning or itching sensation; local paresthesia such as tingling.
Rare Events (<0.1%)	In rare cases, local anesthetics have been associated with allergic reactions; in the most severe instances, anaphylactic shock. There have also been rare cases of discrete local lesions at the application site, described as purpuric or petechial, especially after longer application times in children with atopic dermatitis or molluscum contagiosum. Corneal irritation after accidental eye exposure. Prilocaine in high doses may cause an increase in the methemoglobin level particularly in conjuction with methemoglobin-inducing agents (e.g., sulfonamides) (see 5 OVERDOSAGE).
Very Rare Events (<0.01%)	In very rare cases, central nervous system toxicity (e.g. convulsion, dizziness, loss of consciousness, somnolence) and cardiovascular collapse (e.g. cardiac arrest, hypoxia, respiratory arrest) have occurred after very high doses of EMLA.
Genital Mucosa	
Common Events (>1%)	Application site: transient local reactions such as erythema (redness), edema and paleness; local sensations, e.g., an initial, usually mild, burning sensation, itch or warmth.
Uncommon Events (>0.1% and <1%)	Application site: local paresthesia such as tingling
Rare Events (<0.1%)	In rare cases, local anesthetics have been associated with allergic reactions; in the most severe instances, anaphylactic shock.
Leg Ulcer	
Common Events (>1%)	Transient local reactions at the application site such as paleness, erythema (redness) and edema. Skin sensations, e.g., an initial usually mild burning, itch or warmth at the application site.
Uncommon Events (>0.1% and <1%)	Skin irritation at the application site.
Rare Events (<0.1%)	In rare cases, local anesthetics have been associated with allergic reactions; in the most severe instances, anaphylactic shock.

8.5 Post-Market Adverse Reactions

During post-marketing experience serious and life threatening systemic adverse events, including methaemoglobinaemia, central nervous system toxicity and cardiovascular collapse, have occurred when EMLA cream was applied to large areas of skin for topical analgesia during cosmetic procedures (e.g., laser depilation) (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Lidocaine is mainly metabolized in the liver to its two major pharmacologically active metabolites, monoethylglycinexylidine (MEGX) and glycinexylidine (GX), by CYP1A2 and CYP3A4 and has a high hepatic extraction ratio. Prilocaine is mainly metabolized to o-toluidine in the liver, by unestablished mechanisms. Only a small proportion (2-5%) of lidocaine and prilocaine is excreted unchanged in the urine. The hepatic clearance of lidocaine, and probably prilocaine, is expected to depend largely on blood flow.

With the low systemic exposure to lidocaine and prilocaine and short duration of topical application of EMLA (lidocaine and prilocaine), metabolic drug-drug interactions of clinical significance with lidocaine or prilocaine are unlikely.

Clinically relevant pharmacodynamic drug interactions may occur with EMLA and other local anesthetics or structurally related drugs, and Class I and Class III antiarrhythmic drugs due to additive effects.

Metabolism of prilocaine can accentuate the formation of methemoglobin. Co-administration of EMLA and other methemoglobin-inducing agents to patients 12 months of age or younger may result in clinical signs of methaemoglobinaemia (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS; 9 DRUG INTERACTIONS; 8 ADVERSE REACTIONS; 14 CLINICAL TRIALS).

9.3 Drug-Behavioural Interactions

Interactions of lidocaine and prilocaine with behavioural risks have not been established.

9.4 Drug-Drug Interactions

Drug Class	Source of Evidence	Effect	Clinical Comment
Local anesthetics and amide-type local anesthetics (e.g. antiarrhythmics such as mexiletine)	T	Additive effect	Large doses of EMLA Cream and EMLA Patch should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics.
Class 1 antiarrhythmic drugs (e.g. mexiletine)	T	Additive and potentially synergistic	Class 1 antiarrhythmic drugs (e.g. mexiletine) should be used with caution since the toxic effects are additive and potentially synergistic. Monitor for signs of overdose (see 5 OVERDOSAGE).
Class III antiarrhythmic drugs (e.g. amiodarone)	CT	Potential pharmacodynamic or pharmacokinetic interactions or both Additive effect	Plasma concentration of lidocaine may be increased following administration of a therapeutic dose of intravenous lidocaine to patients treated with amiodarone. Symptoms of lidocaine toxicity in patients treated concomitantly with lidocaine and amiodarone (see 5 OVERDOSAGE). Patients treated with Class III antiarrhythmic drugs (e.g. amiodarone) should be kept under close surveillance and ECG monitoring should be considered.
Cimetidine or beta-blockers (e.g. Atenolol, Propranolol, Nodolol)	T	Reduce the clearance of lidocaine and cause potentially toxic plasma concentrations	When lidocaine is given in repeated high doses over a long time period. Such interactions are not expected to be clinically relevant when lidocaine (e.g., EMLA cream) is used for short term treatment at recommended doses.

Drug Class	Source of Evidence	Effect	Clinical Comment
Methemoglobin-inducing agents (e.g. sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine)	C	Methaemoglobinaemia	Patients treated concomitantly with EMLA may induce the formation of methemoglobin and result in overt clinical signs of methaemoglobinaemia (see 2 CONTRAINDICATIONS; 5 OVERDOSAGE; 7 WARNINGS AND PRECAUTIONS).
Acetaminophen	C	Methaemoglobinaemia	Shown to induce methemoglobin formation *in vitro* and in animals. In humans, methemoglobin formation is rare at therapeutic doses and overdoses (see 5 OVERDOSAGE; 8.2 Clinical Trial Adverse Reactions).

9.5 Drug-Food Interactions

Interactions of lidocaine and prilocaine with food have not been established.

9.6 Drug-Herb Interactions

Interactions of lidocaine and prilocaine with herbs have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions of lidocaine and prilocaine with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

EMLA (Eutectic Mixture of Local Anesthetics) (lidocaine and prilocaine) is a 1:1 oil/water emulsion of a eutectic mixture of lidocaine and prilocaine bases. Dermal analgesia is a result of the migration of lidocaine and prilocaine into the epidermal and dermal layers of the skin followed by the accumulation of these agents in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are both amide-type local anesthetic agents. They stabilize the neuronal membrane preventing the initiation and conduction of nerve impulses, thereby effecting local anesthetic action. EMLA provides dermal analgesia; the depth of which depends upon the application time and the applied dose. Analgesia may be less for deeper structures.

10.2 Pharmacodynamics

EMLA may produce a transient biphasic vascular response involving initial vasoconstriction followed by vasodilation at the application site (see 8 ADVERSE REACTIONS). In patients with atopic dermatitis, a shorter biphasic response involving initial vasoconstriction followed by vasodilation may be seen. Erythema may be observed after 30 to 60 minutes.

10.3 Pharmacokinetics

Absorption:
Systemic absorption of lidocaine and prilocaine from EMLA is dependent upon several factors, including: the applied dose, area of application and duration of application. Additional factors include thickness of the skin (which varies in different areas of the body), vascularity of the skin in the area of application, the presence of any condition in which the skin is not healthy and intact (e.g. sunburn, rash), and shaving. Following application to leg ulcers, the characteristics of the ulcers may also affect the absorption.

Distribution & Metabolism:
Prilocaine has a larger distribution volume than lidocaine which results in lower plasma concentrations of prilocaine when equal amounts of prilocaine and lidocaine are administered. At concentrations produced by application of EMLA, lidocaine is approximately 60-80% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 μg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins.

There is considerable inter-subject variability in lidocaine and prilocaine plasma levels. In pre-marketing studies, all plasma levels of lidocaine and prilocaine after topical administration of

EMLA products were found to be below 1.2 µg/mL. These are below the levels associated with systemic toxicity (5 µg/mL). (see 14 CLINICAL TRIALS).

It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including ortho-toluidine and N-n-propylalanine.

Elimination:
The half-life of lidocaine elimination from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, ±24 SD, n=13). More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. The systemic clearance is 10 to 20 mL/min/kg (mean 13, ±3 SD, n=13). The elimination half-life of prilocaine is approximately 10 to 150 minutes (mean 70, ±48 SD, n=13). The systemic clearance is 18 to 64 mL/min/kg (mean 38, ±15 SD, n=13).

Special Populations and Conditions

- **Atopic Dermatitis**

  It is well known that patients with atopic dermatitis show abnormal vascular reactions to pharmacological stimuli. In patients with atopic dermatitis, percutaneous absorption of EMLA is more rapid and greater than in normal skin. In two adult patients, within one hour after application of 4-6 g EMLA to a 25 cm^2 area of the forearm, lidocaine and prilocaine plasma levels were higher than those observed in normal skin. However, in these patients, the systemic plasma levels were 100 times lower than those associated with toxicity. Dermatological procedures were not performed in the above patients.

  Postmarketing data and limited efficacy and safety data from clinical trials that included a small number of pediatric patients with atopic dermatitis undergoing curettage of molluscum contagiosum indicate that a shorter application time no more than 30 minutes should be used (see 7 WARNINGS AND PRECAUTIONS). Application times of longer than 15 minutes in pediatric patients with atopic dermatitis have resulted in an increased incidence of local vascular reactions, particularly application site redness and edema, and in some cases petechia and purpura.

  Caution is advised when applying EMLA to patients with atopic dermatitis (see 7 WARNINGS AND PRECAUTIONS).

- **Geriatrics**
  There are insufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA (see 7.1.4 WARNINGS AND PRECAUTIONS, Geriatrics).

  During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients. (see 7.1.4 WARNINGS AND PRECAUTIONS, Geriatrics)

11 STORAGE, STABILITY AND DISPOSAL

EMLA Cream (lidocaine and prilocaine) in aluminium tubes should be stored at room temperature (15-30°C). Protect from freezing. EMLA Cream should be discarded within 30 days after opening the tube. Discard the tube with any remaining contents after each occasion that a patient has been treated with EMLA Cream on leg ulcers. Return any unused EMLA Cream to the pharmacist.

EMLA Patch (lidocaine and prilocaine) should be stored at room temperature (15-30°C). Protect from freezing. Single use. Do not reuse.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance: Lidocaine

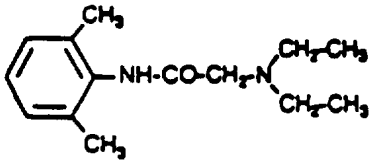
Proper name: lidocaine

Chemical name: 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide

Molecular formula: $C_{14}H_{22}N_2O$

Molecular mass: 234.3 g/mol

Structural formula:



Physicochemical properties:

Description:	White to almost white crystalline powder
Solubility (20°C):	In water: practically insoluble In alcohol: very soluble In ether: freely soluble In methylene chloride: very soluble
Boiling point:	146°C at 1 mm Hg 166°C at 3 mm Hg
pKa:	7.9

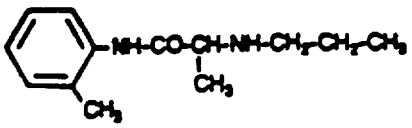
Drug Substance: prilocaine

Proper name: prilocaine

Chemical name: N-(2-methylphenyl)-2-(propylamino)-propanamide

Molecular formula and molecular mass: $C_{13}H_{20}N_2O$, 220.3 g/mol

Structural formula:



Physicochemical properties:

Description:	White to almost white crystalline powder
Solubility (20°C):	In water: slightly soluble In ethanol: very soluble In acetone: very soluble
Boiling point:	156°C to 158°C at 1 mm Hg
pKa:	7.9

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

EMLA Cream

Topical Analgesia in Adults

- Intact Skin

  Local analgesia of intact skin is achieved after a 60-minute application under an occlusive dressing. The analgesic efficacy and the depth of skin analgesia have been shown to increase with application times up to 120 minutes. The duration of analgesia after a 1-2 hour application is at least 2 hours. As the analgesic effectiveness of the cream gradually dissipates once applied, there is no benefit to application times longer than 5 hours.

  The depth of analgesia, as measured by the insertion of a needle through the skin, is about 3 mm after a 60-minute application, about 4 mm after a 90-minute application and about 5 mm after a 120-minute application.

  Both the analgesic efficacy and depth continue to increase after the removal of the cream from the skin surface, i.e., after a 60-minute application time to the dorsum of the hand, the analgesic efficacy continued to increase for 15 minutes, and persisted for a total of 75 minutes after removal of the cream.

  EMLA Cream (lidocaine and prilocaine) is equally effective and has the same anesthetic onset time across the range of light to dark pigmented skin (skin types I - IV).

  The systemic absorption of lidocaine and prilocaine was evaluated in 16 healthy volunteers after topical administration of EMLA cream. Eight volunteers received 60 g of EMLA applied to an area of 400 cm2 on the thigh under an occlusive dressing for

3 hours. Another 8 subjects had the same amount applied for 24 hours to represent an unintended prolonged application.

Maximum plasma concentrations (mean 0.12 μg/mL for lidocaine and 0.07 μg/mL for prilocaine), were reached approximately 2-6 hours after the application. Individual plasma concentrations of lidocaine and prilocaine were low throughout the study and did not exceed 0.4 μg/mL, which is far below potentially toxic levels of 5 μg/mL.

Following the application of approximately 150 g of EMLA cream to intact skin areas of up to 1,300 cm2, for up to 3 hours duration, the highest individual plasma levels observed were 1.1 μg/mL lidocaine and 0.2 μg/mL prilocaine. These plasma levels remained below the levels at which symptoms of toxicity would be expected (5 μg/mL either agent).

Following application to the face (10 g/100 cm2 for 2 hours), maximum plasma levels (mean 0.16 μg/mL lidocaine and 0.06 μg/mL prilocaine) were reached after approximately 1.5-3 hours.

- Superficial Skin Procedures
  In an open split skin grafting study, blood samples were drawn immediately after removal of EMLA cream and 3 hours later. The maximum plasma concentrations of lidocaine and prilocaine immediately after removal of the cream were 1.1 μg/mL and 0.2 μg/mL, respectively.

- Genital Mucosa
  Absorption from the genital mucosa is more rapid, i.e., maximum plasma concentrations are reached 20-45 minutes after application as opposed to 1.5-6 hours after application to intact skin. As a result, onset time and duration of action are shorter than after application to intact skin.

- Leg Ulcers
  In studies, EMLA was shown to reduce the number of cleansing sessions required to achieve a clean ulcer compared to placebo cream and reduced the post-cleansing pain up to 4 hours after debridement. No negative influence on ulcer healing or bacterial flora has been observed.

  In clinical studies, the repeated use of EMLA cream prior to the cleansing of leg ulcers has been evaluated in 88 patients. Application of 1 to 10 g/10 cm2 for 30-60 minutes, up to 15 times within a 1 - 2 month period, resulted in no apparent loss of analgesic effect or increase in local reactions. The maximum observed plasma levels for lidocaine, monoglycinexylidide and 2,6-xylidine were low at 0.41, 0.03 and 0.01 μg/mL, respectively, with no apparent accumulation. The maximum observed plasma levels for prilocaine and o-toluidine were 0.08 μg/mL and 0.01 μg/mL, respectively.

Following the application of 5 to 10 g of EMLA to leg ulcers 15 to 64 cm^2 in size, for 30 minutes, maximum individual plasma concentrations of lidocaine and prilocaine ranged from 0.05 to 0.84 µg/mL, 0.02 to 0.08 µg/mL, respectively. These maximum concentrations were reached within 1 to 2.5 hours.

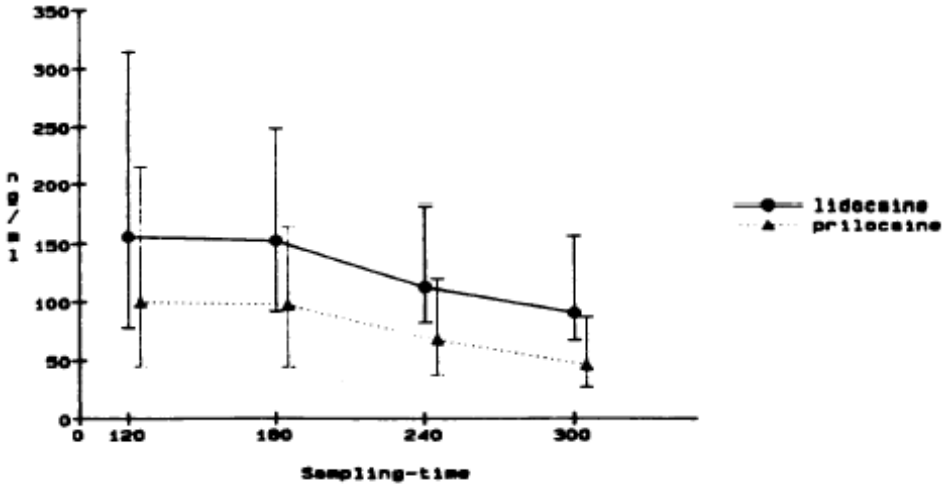
After prolonged application (24 h) of 1 g EMLA/10 cm^2 to leg ulcers 50 to 100 cm^2, maximum plasma concentrations of lidocaine and prilocaine ranged from 0.18 to 0.7 µg/mL and 0.06 to 0.28 µg/mL, and were observed 2-4 hours (in one patient 6- 8 hours) after administration.

In clinical studies, the repeated use of EMLA cream prior to the cleansing of leg ulcers has been evaluated in 88 patients. Application of 1 to 10 g/10 cm^2 for 30-60 minutes, up to 15 times within a 1 - 2 month period, resulted in no apparent loss of analgesic effect or increase in local reactions. The maximum observed plasma levels for lidocaine, monoglycinexylidide and 2,6-xylidine were low at 0.41, 0.03 and 0.01 µg/mL, respectively, with no apparent accumulation. The maximum observed plasma levels for prilocaine and o-toluidine were 0.08 µg/mL and 0.01 µg/mL, respectively.

Topical Analgesia in Pediatrics (including neonates)

- Intact Skin
  Plasma concentrations of lidocaine and prilocaine were measured in 72 children after topical application of EMLA cream to intact skin. In two of the six studies, venous blood samples were drawn before application of the cream and at 120, 180, 240 and 300 minutes after. In the first study (n = 10) where the patient ages were lower (2- 3 yrs), maximum plasma concentrations of lidocaine and prilocaine were 0.315 µg/mL and 0.215 µg/mL, respectively.

Figure 1 **Venous Plasma Concentrations of Lidocaine and Prilocaine after Epicutaneous Application of 10 g EMLA Cream for 120 minutes to Children 2-3 years of age (mean, max. and min. value, n = 10).**



In the second study (n = 10), where the patient ages were higher (6-8 yrs), plasma levels were 0.299 µg/mL and 0.110 µg/mL, respectively, for lidocaine and prilocaine.

The remaining 4 studies evaluated the efficacy of EMLA cream.

Table 6 **Maximum Individual Plasma Concentrations of Lidocaine and Prilocaine Following Application of EMLA Cream in Children and Infants.**

Age	n	EMLA Cream Dose/Area (g/cm^2)	Application Time (h)	Maximum Plasma Concentrations (µg/mL)		Time from Start of Application to Max Plasma Concentration (h)
				Lidocaine	Prilocaine	
Neonates (< 3 mos)	38	1 g/10 cm^2	1	0.135	0.107	4-6
Infants (3-12 mos)	22	2 g/16 cm^2	4	0.155	0.131	4
Children (2-3 years)	10	10 g/100 cm^2	2	0.315	0.215	2
Children (6-8 years)	10	10-16 g/ 100-160 cm^2	2	0.299	0.110	2-2.5

a Data in children 4-5 years old are not available.

In six clinical trials conducted in full-term infants below 3 months of age (n = 147 total), EMLA cream was applied to several sites, including the heel and the prepuce of the penis.

The dose applied was 0.5 - 1.0 g for 1 hr in five studies, and 2.0 g for 4 hrs in one study. MetHb plasma levels were measured in all six studies, while lidocaine and prilocaine levels were measured in five.

MetHb levels after EMLA application were increased over placebo levels, with the maximum percentage levels occurring most frequently at 8 hours post-application. The levels in these studies never approached potentially toxic levels, as the highest MetHb level reported was 3.37%, and the maximum increase from baseline reported was 2.19%, both reported in the study using the highest dose of EMLA (2 g applied for 4 hours).

In all five studies, both mean and individual plasma concentrations of lidocaine and prilocaine remained well below toxic levels; individual maximum values of lidocaine and prilocaine were 0.412 and 0.05 µg/mL, respectively.

- Superficial Skin Procedures
  In eleven clinical trials investigating the efficacy of the topical application of EMLA cream to the intact skin of infants and children (total n = approximately 1019; birth to 11 years), EMLA cream was found to be superior to placebo in the reduction of pain associated with superficial skin procedures, based on scores from Visual Analogue Scales, Verbal Scales (three-and four-point), the Modified Behavioural Pain Scale and the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS).

- In seven of the eleven clinical trials, the efficacy of EMLA cream in relieving the pain of immunization was investigated. EMLA has been shown to significantly reduce the pain associated with the following vaccines: MMR (Measles-Mumps-Rubella); DPTP (Diptheria-Pertussis-Tetanus-Poliovirus); *Hemophilus influenzae* b; Hepatitis B; Fluzone® and tetanus. The efficacy of EMLA in reducing the pain of any other vaccine is unknown (see 14.1 Clinical Trials by Indication; Vaccination for further information on the use of EMLA prior to vaccination).

- Circumcision
  Data from three randomized, controlled studies in infants undergoing circumcision indicate that EMLA cream may be more effective than placebo in attenuating the behavioural and physiologic indicators of neonatal pain during circumcision, but it does not entirely prevent infant distress.

  The studies involved a total of 78 EMLA-treated and 80 placebo-treated neonates.

  In these studies, distress was measured at 9 or 13 time points throughout the procedure, and the values compared to a baseline point immediately prior to the procedure.

In one study, (EMLA dose was 0.5 g applied to the prepuce for approximately 1 hour), no significant differences in distress levels were found between groups using either the Neonatal Facial Coding System (NCFS), or various physiological parameters, such as heart rate and oxygen saturation.

In both the remaining two studies, under similar conditions of use (0.5 g, and 1.0 g, applied to the prepuce for approximately 1 hour), there was a significant overall mean effect of EMLA over placebo (2 to 20 % difference) for NFCS, heart rate, and time spent crying.

In these studies, 1.0 g of EMLA cream applied to the prepuce of the penis for 1 hour was well tolerated. The incidence and type of local reactions were not different from those for other age groups, and there were no clinical signs of methaemoglobinaemia.

EMLA Patch

- Needle Insertion
  For pain relief in venepuncture, EMLA Patch has been shown to be efficacious and safe (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING). There have been no observed local skin reactions of clinical significance.

- Vaccination
  [Note: MMR: Measles-Mumps-Rubella; DPTP: Diptheria-Pertussis-Tetanus-Poliovirus]

  EMLA has been shown to effectively reduce the pain associated with vaccination in all age groups (see 14 CLINICAL TRIALS; Topical Analgesia in Pediatrics (including neonates); Superficial Skin Procedures). In order to determine if treatment with EMLA prior to immunization interferes with the immune response, two pivotal, double-blind, placebo-controlled trials have been performed (total n = 325).

  In the two pivotal, double-blind, placebo-controlled trials, 325 infants (from birth to 15 months) were treated with EMLA or placebo patch prior to vaccination with MMR, DPTP, *Haemophilus influenzae* b or Hepatitis B vaccines. In both studies, there were no differences between the EMLA and placebo-treated groups in: 1. the proportion of subjects achieving protective antibody levels for any vaccine constituent; 2. the proportion of subjects who achieved a ≥ 4 fold increase in antibodies to any vaccine constituent and 3. the geometric mean antibody levels for any vaccine constituent.

  The results from the pivotal trials have shown that the use of EMLA prior to vaccination with MMR, DPTP, *Haemophilus influenzae* b and Hepatitis B vaccines is safe and efficacious. No deleterious effect on the immune response has been demonstrated in connection with EMLA use during clinical trials.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology
The acute toxicity of lidocaine, prilocaine, and a 1:1 mixture of lidocaine:prilocaine were studied in Sprague-Dawley rats and NMRI mice. The LD_{50} values obtained at Days 1 and 14 following a single administration of the test compound and the routes of administration used are summarized in Table 7.

Table 7 Acute Toxicity in Rats and Mice

Animal		Sex	Number	Route of Administration	Test Compound	LD_{50} (mg/kg) Day 1, Day 14
Species	Strain					
Rat	Sprague-Dawley	M	6	i.v.	lidocaine HCl	24.2
Rat	Sprague-Dawley	M	6	i.v.	prilocaine HCl	44.7
Rat	Sprague-Dawley	M	6	i.v.	1:1 prilocaine HCl/ lidocaine HCl	24-35
Mouse	NMRI	M	10	i.v.	lidocaine HCl	63.0
Mouse	NMRI	M	10	i.v.	prilocaine HCl	90.9
Mouse	NMRI	M	10	i.v.	1:1 prilocaine HCl/ lidocaine HCl	67.6
Rat	Sprague-Dawley	M	6	s.c.	Lidocaine base	>1029
Rat	Sprague-Dawley	M	6	s.c.	Prilocaine base	>925
Rat	Sprague-Dawley	M	6	s.c.	1:1 lidocaine base: prilocaine base	>865
Rat	Sprague-Dawley	M	6	s.c.	Placebo	no mortalities

After administration of high doses of either lidocaine or prilocaine alone or in combination effects were seen on the central nervous and cardiovascular systems.

Dermal application is the most relevant route of administration for purposes of testing EMLA (lidocaine and prilocaine) acute toxicity. An EMLA cream was formulated in much higher

concentrations (50 mg/mL of each agent) and applied for a longer period of time in a preliminary test.

The results showed that dermal absorption of both compounds was accentuated, blood concentrations were higher but no symptoms were observed in any animal.

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.

The acute toxicity of EMLA cream was determined in 6 New Zealand white rabbits (3 males, 3 females) after a single dermal administration.

The test formulation was applied under a semi-occlusive dressing, for 24 hours, on at least 10% of the total skin area of each animal. The maximum possible concentration (43%) and amount (10 g) of EMLA cream were used, resulting in a dose of approximately 1200 mg/kg body weight or 21.5 mg/cm^2 skin. The animals were observed for 14 days.

No adverse reactions or deaths were seen, although all animals showed slightly reduced body weights after 14 days. No skin irritation was observed following the application of these large doses of EMLA cream.

Blood samples were withdrawn for analysis of lidocaine and prilocaine both during and after application. The concentration of prilocaine was about 45% to 70% of the lidocaine level. Both concentrations rose rapidly, showed a steady state pattern between 3 and 25 hours, and then fell fairly rapidly, with only small amounts detectable after 49 hours. The maximum plasma concentrations obtained ranged from 1.13 µg/mL to 2.23 µg/mL for lidocaine, and 0.54 µg/mL to 1.52 µg/mL for prilocaine.

The general toxicity of EMLA was studied in dogs following rectal administration for 1 month. Thirty Beagles were divided into 5 groups, 3 males and 3 females in each group (Table 8).

Table 8 General Toxicity of EMLA in Dogs

Group	Compounds	Daily Dose of EMLA	
		mg/kg	mL/kg
1	Untreated Control	-	-
2	Placebo	-	-
3	EMLA 2%	5	0.25
4	EMLA 2%	12	0.60
5	EMLA 5%	12.5	0.25

Group 1 was not treated with a test or a placebo formulation, but was identical to the other groups in all other respects. Group 2 received 0.25 mL/kg of the cream base for EMLA 5% cream.

The formulations were deposited approximately 5 cm into the rectal lumen using a rubber tube. Immediately before each dose the dogs were purged with a physiological saline solution. Clinical signs, food consumption, body weight and rectal temperature were recorded regularly. Electrocardiography and ophthalmoscopy were performed.
The blood plasma concentrations of the components in EMLA (lidocaine and prilocaine) were determined. Hematology, blood chemistry and urinalysis were performed. Complete autopsies were performed on all animals, organ weights were recorded, and tissue samples were examined microscopically.

No signs of clinical dysfunction related to the treatment were seen during the study. The hematology, blood chemistry and urinalysis did not indicate any effect caused by the treatment. The pathologic investigation did not reveal any changes that could be related to treatment.

Carcinogenicity

No long-term animal studies evaluating carcinogenic potential of EMLA or its active ingredients, lidocaine or prilocaine, have been conducted.

Chronic oral toxicity studies of o-toluidine, a metabolite of prilocaine, in mice (150- 2400 mg/kg) and rats (150-800 mg/kg) have shown that o-toluidine is a carcinogen in both species at all doses tested. A non-carcinogenic dose in rats or mice has not been established. The lowest tumor-inducing dose tested in animals (150 mg/kg) corresponds to approximately 30 times the amount of o-toluidine to which a 50 kg subject would be exposed following the application of 60 g of EMLA cream for 24 hours on the intact skin, assuming an extent of absorption of 30%, and 100% conversion to o-toluidine. Based on a yearly exposure (once daily dosing with o-toluidine in animals and 5 treatment sessions with 60 g EMLA cream in humans), the safety margins would be approximately 2200 times when comparing the exposure in animals to man.

Genotoxicity

Lidocaine and prilocaine did not show any evidence of mutagenic potential in either of the *in vitro* or *in vivo* tests performed - Ames Salmonella/mammalian microsome mutagenicity test and mouse micronucleus test. In addition, lidocaine did not induce chromosome aberrations in human lymphocytes.

A metabolite of prilocaine, o-toluidine (0.5 µg/mL), showed positive results in E. coli DNA repair and phage-induction assays. Urine concentrates from rats treated with o-toluidine

(300 mg/kg orally) were mutagenic for *Salmonella typhimurium* with metabolic activation. Several other tests, including reverse mutations in five different *Salmonella typhimurium* strains with or without single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Conflicting results were seen in the bacterial mutagenicity tests of 2,6-xylidine, a metabolite of lidocaine. Genotoxic effects were seen in mammalian cells treated with toxic concentrations of 2,6-xylidine; in mouse lymphoma cells (elevated mutation frequency), Chinese hamster ovary cells (chromosome aberrations and sister chromatid exchanges) and BALB/c-3T3 cells (increased cell transformation).

A chronic oral toxicity study of the metabolite 2,6-xylidine (0, 14, 45, 135 mg/kg) administered in feed to rats showed that there was a significantly greater incidence of nasal cavity tumors in male and female animals that had daily oral exposure to the highest dose of 2,6-xylidine for 2 years. The lowest tumor-inducing dose tested in animals (135 mg/kg) corresponds to approximately 60 times the amount of 2,6-xylidine to which a 50 kg subject would be exposed following the application of 60 g of EMLA cream for 24 hours on the intact skin, assuming an extent of absorption of 15%, and 80% conversion to 2,6-xylidine. Based on a yearly exposure (once daily dosing with 2,6-xylidine in animals and 5 treatment sessions with 60 g EMLA cream in humans), the safety margins would be approximately 4700 times when comparing the exposure in animals to man.

Risk Assessments comparing the calculated maximum human exposure to o-toluidine and 2,6- xylidine from intermittent use of lidocaine and prilocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

Reproductive and Developmental Toxicology

In two teratogenicity studies in rats subcutaneous administration of a 1:1 w/w mixture of lidocaine HCl and prilocaine HCl in doses up to 40 + 40 mg/kg (150 µmol/kg lidocaine HCl + 160 µmol/kg prilocaine HCl) did not affect organogenesis or early fetal development.
A slight decrease in body weight gain was observed in the dams at the highest dose level. A dose-related incidence of necrosis at the injection site was observed. Also observed was a slight but dose-related decrease in packed cell volume, hemoglobin concentration and the number of erythrocytes, as well as a slight increase in the number of platelets. All changes were very small. An increase in methemoglobin concentration was observed, however, the increase was very slight and not statistically significant. The local reaction (necrosis) noted at the injection site prevented higher doses being given.

In studies on reproduction toxicity, embryotoxic or foetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit and foetal hydronephrosis 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 or prilocaine 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 embryofoetal dose to the maternal serum concentration is 0.4 to 1.3.

Special Toxicology

Placebo, 5.0, and 10.0% EMLA emulsions were administered (0.25 mL) ocularly, on a single occasion, to 6 rabbits. Eye irritation was examined at both 1 hour and 24 hours after administration and then daily for up to 10 days after treatment. Administration of physiological saline and the placebo emulsion caused a mild and short-lasting irritation which had completely regressed after 48 hours. However, both 5.0 and 10.0% EMLA emulsions produced a severe and long-lasting irritation, including marked conjunctival hyperemia, swelling, fluid and exudate discharge and iris reaction, but not corneal damage. These symptoms gradually disappeared 2-10 days after administration. The reaction observed after a single ocular administration indicates that EMLA emulsion is unsuitable for ocular administration. Furthermore, precautions should be taken when using this emulsion close to the eyes.

PATIENT MEDICATION INFORMATION **TRANSDERMAL PATCH**

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

EMLA® Patch
Lidocaine and Prilocaine Transdermal Patch

Read this carefully before you start taking **EMLA Patch** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EMLA Patch**.

What is EMLA Patch used for?
EMLA Patch is used to temporarily numb small areas of skin that are slightly larger than a two dollar coin or "toonie". It can only be used on healthy, unbroken skin:

- before getting a needle or having blood taken;
- before being vaccinated with only the following vaccines:
  - MMR (Measles-Mumps-Rubella)
  - DPTP (Diptheria-Pertussis-Tetanus-Poliovirus)
  - *Haemophilus influenzae* b
  - Hepatitis B.

How does EMLA Patch work?
EMLA Patch contains the drugs lidocaine and prilocaine. These drugs are anesthetics and they cause a temporary numbness of the skin where the patch is applied.

What are the ingredients in EMLA Patch?
Medicinal ingredients: lidocaine 2.5% and prilocaine 2.5%
Non-medicinal ingredients: carboxypolymethylene, polyoxyethylene hydrogenated castor oil, purified water, sodium hydroxide.

The transdermal patch is made from: cellulose and cotton disc, polyethylene foam with acrylate adhesive, polyamide/aluminium/plastic and polypropylene/aluminium/plastic laminates. The patch is made with natural rubber latex.

EMLA Patch comes in the following dosage forms:
1 g transdermal patches

Each transdermal patch has a tan-coloured adhesive tape with a round white pad in the centre.

Do not use EMLA Patch if:

- you are allergic to lidocaine, prilocaine, any other "-caine" type anesthetics, or any of the non-medicinal ingredients in the product
- you have a blood disorder called methaemoglobinaemia
- it is for infants who are 12 months of age or younger and are taking drugs that may cause the blood disorder called methaemoglobinaemia (e.g. sulphonamides, used to treat infections)
- it is for infants who were born after less than 37 weeks of pregnancy
- it is for medical procedures that aren't done in a hospital and that require many EMLA patches over a large body area

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EMLA Patch. Talk about any health conditions or problems you may have, including if you:

- have glucose-6-phosphate dehydrogenase deficiency
- have ever had a bad, unusual or allergic reaction to lidocaine or prilocaine, also available under brand names such as Xylocaine® (lidocaine) and Citanest® (prilocaine)
- might be sensitive or allergic to other ingredients of the patch
- have an infection, skin rash or cut at, or near, the area where you want to apply EMLA Patch
- have atopic dermatitis, eczema or any other skin problems or diseases
- have severe kidney or liver disease
- are pregnant or trying to become pregnant
- are breastfeeding. If you are breastfeeding ELMA Patch should not be applied on or near the breasts.
- are 65 years of age or older.

Other warnings you should know about:

- **Risk of serious side effects**
  Be careful to apply no more than the maximum recommended dose of EMLA Patch. Serious and life threatening side effects have occurred when EMLA Patch was not used properly. This includes a serious blood disorder called methaemoglobinaemia, where the blood brings less oxygen to your body. If you develop this condition, you may have brownish or greyish skin especially around lips and nails. If your condition worsens, you can have:
  - Heart problems leading to a heart attack, difficulty breathing or not breathing
  - Problems with your central nervous system such as:
    - seizures
    - dizziness
    - fainting
    - feeling drowsy

Other symptoms you may have include:

- numbness of the tongue
- light-headedness
- confusion
- headache
- sight or hearing problems
- vomiting
- dizziness
- weakness
- nervousness
- unusual sweating
- trembling

If you get any of these side effects, stop taking EMLA Patch and get medical help right away.

- Children are at greater risk for serious side effects. Always follow your healthcare professional's instructions for using EMLA Patch, especially in young children and infants under 3 months old. Make sure young children don't accidentally swallow used EMLA patches. EMLA Patch should not be used on the genitals of children or infants.

- EMLA Patch should not be used close to the ear or eyes because it can cause damage.

Driving and using machines:

- Know how you feel after using EMLA Patch before you drive or use heavy machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EMLA Patch:

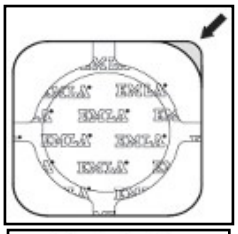
- medicines for heart rhythm problems (e.g. mexilitine, amiodarone)
- other anesthetics used to numb the skin
- other medicines which may cause methaemoglobinaemia, including: sulfonamides, acetanilide, aniline dyes, benzocaine (or other "-caine" type anesthetics), chloroquine, dapsone, naphthalene, nitrates or nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine and high doses of acetaminophen

How to take EMLA Patch:

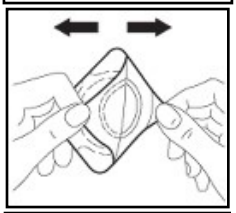
- Be careful not to apply more EMLA Patch or replace it more frequently than your healthcare professional recommended. Serious and life-threatening side effects have occurred when EMLA Patch was not used properly and more than the recommended amounts were used

- Be sure to only put EMLA Patch on unbroken skin
- Do not put EMLA Patch in your mouth or swallow it. Take special care to ensure that infants and young children do not put the patch in their mouth. If EMLA Patch is accidentally swallowed, call your healthcare professional
- Do not re-use EMLA Patch
- The numbing effect of EMLA Patch starts working about 1 hour after it is applied. You may still feel pressure and touch in the area where you applied EMLA Patch. The numbness of the skin may continue to increase after the patch is removed, and will last for at least 2 hours following a 1-2 hour application
- Tell your healthcare professional if you feel that the effect of EMLA Patch is too strong or too weak

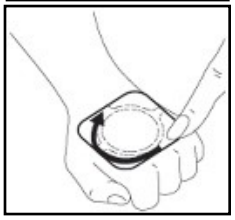
Steps to apply EMLA Patch:



1. Make sure your skin is clear and dry. Take hold of the aluminium flap at the corner of the patch and bend it back.



2. While holding the aluminium flap, take hold of the corner of the tan-coloured patch layer. Pull the two layers apart, separating the adhesive surface from the aluminium paper backing. Do not touch the white, round pad which contains the anaesthetic.



3. Apply EMLA Patch so that the white, round pad containing the anaesthetic covers the area to be treated. Press **firmly** only around the **edges** of the patch to ensure a good adhesion to the skin. Press **gently** on the **centre** of the patch to ensure it comes into contact with the skin. It is important to make sure that the patch is firmly secured. If not, it may not be effective, or others might be accidentally exposed to the medication.

4. Mark the time of application directly on the patch with a ballpoint pen. EMLA Patch must be applied for at least 1 hour before the start of the procedure. Leave the patch on for as long as your healthcare professional recommended, at least for 1 hour. Be careful that the patch doesn't come off during the wait.

5. Remove EMLA Patch and clean the area thoroughly before the procedure. If you are applying the EMLA Patch for a procedure to be performed by a healthcare professional, you should leave it on for the healthcare professional to remove, unless instructed otherwise.

6. Throw away used EMLA Patch by carefully folding it in half so the adhesive side sticks to itself. Dispose of the used patch in the garbage out of the reach and sight of children and pets.

Usual Dose:
The dosing for adults and children is listed below. To help prevent side effects, your healthcare professional may need to adjust the usual dose if you:

- are elderly
- are acutely ill
- have severe liver or kidney disease
- are being treated with other anesthetics or certain heart drugs (e.g. mexilitine, amiodarone)
- have skin conditions such as atopic dermatitis

Adults
Apply the quantity of EMLA Patch prescribed by your healthcare professional to the specific skin area at least 1 hour before the procedure. You will not get any added benefit from leaving EMLA Patch on for longer than 5 hours.

Children
Observe your child closely during and after use of topical anesthetics, as they are at greater risk than adults for serious side effects.

When using EMLA Patch for your child's pain relief, remember it is also very important to provide comfort and emotional support.

The dosing below is based on age. Your healthcare professional may recommend a different dose for your child if their weight is less than what is typical for their age category.

- **Infants Under 3 Months:**
  Do not apply the EMLA Patch to infants under 3 months of age unless a healthcare professional tells you to do so. Infants under 3 months of age are at a higher risk than older children for methaemoglobinaemia.

  Apply one patch on the specific skin area for 1 hour. Do not use more patches and do not leave EMLA Patch on the skin for longer than 1 hour.

The size of the patch makes it less suitable for use on certain parts of the body in neonates and infants.

- **Infants Between 3 and 12 Months of Age:**
  Apply one or two patches on the specific skin area for about 1 hour. Do not use more patches and do not leave EMLA Patch on the skin for more than 4 hours.

- **Children Between 1-6 Years:**
  Apply one or more patches on the specific skin area for at least 1 hour. Do not use more than 10 patches and do not leave on the skin for more than 5 hours.

- **Children Between 7-12 Years:**
  Apply one or more patches on the specific skin area for at least 1 hour. Do not use more than 20 patches and do not leave on the skin for more than 5 hours.

Overdose:

If you think you, or a person you are caring for, have taken too much EMLA Patch, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using EMLA Patch?

These are not all the possible side effects you may feel when taking EMLA Patch. If you experience any side effects not listed here, tell your healthcare professional.

Your skin where EMLA Patch was applied may stay numb for up to several hours after you take the patch off. Be careful to avoid hurting your skin until your skin isn't numb anymore. This includes scratching, rubbing or exposing your skin to extreme hot or cold temperatures.

The following side effects can happen to the skin where the patch was applied:

- whitening or redness
- slight swelling or puffiness
- initial burning or itching
- tingling of the skin, warmth
- small red dots or purple spots

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Methaemoglobinaemia: brownish or greyish skin especially around lips and nails.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Eye irritation: if EMLA Patch enters the eye, immediately rinse the eye in water.			✓
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
VERY RARE			
Central nervous system toxicity: seizures, dizziness, fainting, feeling drowsy, loss of consciousness.			✓
Cardiovascular collapse: severe chest pain and pressure, nausea, vomiting, shortness of breath, trouble breathing, stopping breathing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep EMLA Patch well out of the reach and sight of children, even after the patch is removed and put in the garbage.
- Store EMLA Patch at room temperature (15-30°C). Protect from freezing.
- Do not use EMLA Patch after the expiry date on the carton. Remember to return any unused EMLA Patch to your pharmacist.

If you want more information about EMLA Patch:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.aspenpharma.ca, or by calling 1-844-330-1213.

This leaflet was prepared by
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L6M 3E3

Last Revised: April 20, 2022

PATIENT MEDICATION INFORMATION **CREAM**

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

EMLA® Cream
Lidocaine and Prilocaine Cream

Read this carefully before you start taking **EMLA Cream** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EMLA Cream**.

What is EMLA Cream used for?
EMLA Cream is used to temporarily numb the skin. It can be used:

- on healthy, unbroken skin before getting a needle or having blood taken
- on healthy, unbroken skin before minor skin procedures or surgeries
- before being vaccinated with only the following vaccines:
    - MMR (Measles-Mumps-Rubella)
    - DPTP (Diphtheria-Pertussis-Tetanus-Poliovirus)
    - *Haemophilus influenzae* b
    - Hepatitis B
- on the genitals for short surgeries
- for the cleansing of leg ulcers

EMLA Cream should only be used for the uses above. Serious and life-threatening side effects have happened when EMLA Cream was applied to large areas of skin.

How does EMLA Cream work?
EMLA Cream contains the drugs lidocaine and prilocaine. These drugs are anesthetics and they cause a temporary numbness of the skin where the cream is applied.

What are the ingredients in EMLA Cream?
Medicinal ingredients: lidocaine 2.5% and prilocaine 2.5%

Non-medicinal ingredients: carboxypolymethylene, polyoxyethylene hydrogenated castor oil, purified water, sodium hydroxide.

The 5 g EMLA Cream tube also includes dressings. Tegaderm® dressings contain polyether polyurethane films, acrylate agadedhesives and paper liners. These dressings are hypoallergenic and are not made with natural rubber latex.

EMLA Cream comes in the following dosage forms:
Cream: 5 g and 30 g tubes

Do not use EMLA Cream if:

- you are allergic to lidocaine, prilocaine, any other "-caine" type anesthetics, or any of the non-medicinal ingredients in the product
- you have a blood disorder called methaemoglobinaemia
- it is for infants who are 12 months of age or younger and are taking drugs that may cause the blood disorder called methemoglobenima (e.g., sulphonamides, used to treat infections)
- it is for infants who were born after less than 37 weeks of pregnancy

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EMLA Cream. Talk about any health conditions or problems you may have, including if you:

- have glucose-6-phosphate dehydrogenase deficiency
- have ever had a bad, unusual or allergic reaction to lidocaine or prilocaine, also available under brand names such as Xylocaine® (lidocaine) and Citanest® (prilocaine)
- may be sensitive or allergic to other ingredients of the cream or Tegaderm® dressing
- have an infection, skin rash or cut at, or near, the area where you want to apply EMLA Cream
- have atopic dermatitis, eczema or any other skin problems or diseases
- have severe kidney or liver disease
- are pregnant or trying to become pregnant
- are breastfeeding. If you are breastfeeding ELMA Cream should not be applied on or near the breasts
- would like to use EMLA Cream prior to treatment of a leg ulcer(s)
- would like to use EMLA Cream on the genital area of children
- are 65 years of age or older

Other warnings you should know about:

- **Risk of serious side effects**
  Be careful to apply no more than the maximum recommended dose of EMLA Cream. Serious and life-threatening side effects have occurred when EMLA Cream was not used properly. This includes a serious blood disorder called methaemoglobinaemia, where the blood brings less oxygen to your body. If you develop this condition, you may have brownish or greyish skin especially around lips and nails. If your condition worsens, you can have:
  - Heart problems leading to a heart attack, difficulty breathing or not breathing
  - Problems with your central nervous system such as:
    - seizures
    - dizziness
    - fainting
    - feeling drowsy

Other symptoms you may have include:

- numbness of the tongue
- light-headedness
- confusion
- headache
- sight or hearing problems
- vomiting
- dizziness
- weakness
- nervousness
- unusual sweating
- trembling

If you get any of these side effects, stop taking EMLA Cream and get medical help right away.

- Children are at greater risk for serious side effects. Always follow your healthcare professional's instructions for using EMLA Cream, especially in young children and infants under 3 months old. EMLA Cream should not be used on the genitals of children or infants.

- EMLA Cream should not be used close to the ear or eyes because it can cause damage.

Driving and using machines:

- Know how you feel after using EMLA Cream before you drive or use heavy machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EMLA Cream:

- medicines for heart rhythm problems (e.g. mexilitine, amiodarone)
- other anesthetics, used to numb the skin
- other medicines which may cause methaemoglobinaemia, including: sulfonamides, acetanilide, aniline dyes, benzocaine (or other "-caine" type anesthetics), chloroquine, dapsone, naphthalene, nitrates or nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine and high doses of acetaminophen

How to take EMLA Cream:

- Be careful not to apply more EMLA Cream than your healthcare professional recommended. Serious and life-threatening side effects have occurred when EMLA Cream was not used properly and more than the recommended amounts were used.

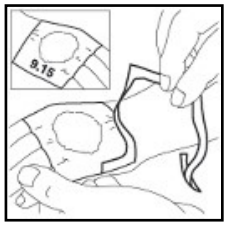
- Be sure to only put EMLA Cream on unbroken skin, except for leg ulcers where it has been prescribed for that condition.
- Do not put EMLA Cream in your mouth or swallow it. If EMLA Cream is accidentally swallowed, call your healthcare professional.
- Do not re-use EMLA Cream dressings once applied.
- The numbing effect of EMLA Cream starts working about 1 hour after it is applied. You may still feel pressure and touch in the area where you applied EMLA Cream. The numbness of the skin may continue to increase after the cream is removed and will last for at least 2 hours following a 1–2-hour application.
- Tell your healthcare professional if you feel that the effect of EMLA Cream is too strong or too weak.

Steps to apply EMLA Cream:

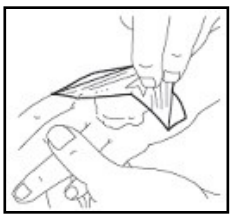
1. Make sure your skin is clean and dry. Apply cream in a thick layer at the site of the procedure. Do **not** rub the cream into the skin.

2. Cover treated area with an air-tight dressing such as Tegaderm® or plastic wrap. Tegaderm® is provided with the 5 g tubes only. If using Tegaderm® remove the center cut-out piece as shown. Peel the paper liner from the paper-framed dressing. It is important to cover EMLA Cream with an air-tight dressing to ensure that the cream penetrates the skin properly and numbness of the area is felt.

3. Carefully cover the EMLA Cream so that you are left with a thick layer of cream underneath the dressing. Do not spread out the cream. Smooth down the dressing edges carefully and make sure it is secure to prevent leakage. If using plastic wrap, hold the dressing in place with adhesive or medical tape and make sure it is air-tight.



4. If using Tegaderm®, remove the paper frame. The time of application can easily be marked directly on the Tegaderm® with a ballpoint pen. If using plastic wrap, mark the time of application on the medical tape that is holding the dressing in place.



5. Keep the dressing and cream on for as long as your healthcare professional recommended, usually at least 1 hour. Remove the dressing and clear the area of excess cream thoroughly before the procedure. If you are applying the EMLA Cream for a procedure to be performed by a healthcare professional, you should leave the dressing on for the healthcare professional to remove, unless otherwise instructed.

6. Throw the plastic wrap or the Tegaderm® in the garbage, out of the reach and sight of children and pets.

Usual Dose:

- The dosing for adults and children is listed below. To help prevent side effects, your healthcare professional may need to adjust the usual dose if you:
    - are elderly
    - are acutely ill
    - have severe liver or kidney disease
    - are being treated with other anesthetics or certain heart drugs (e.g. mexilitine, amiodarone)
    - have skin conditions such as atopic dermatitis
- When applying EMLA Cream, 1 g of cream is the same as a ribbon of cream of about 3.5 cm (1.5 inches).
- Make sure to follow the steps above when you apply EMLA Cream, including covering the cream with an air-tight dressing.

Adults

DOSAGE OF EMLA CREAM ON HEALTHY SKIN

For minor skin procedures/surgeries or when getting a needle or having blood taken:

- apply a thick layer of cream, about half of a 5 g tube (2 g), on an area slightly larger than a two dollar coin or “toonie”.
- leave the EMLA Cream on for at least 1 hour.

For procedures with larger areas, such as skin grafting:

- Your healthcare professional may apply the EMLA Cream when you arrive for your procedure.
- If your healthcare professional told you to put the cream on yourself before the procedure, make sure they clearly explain the size of the area to be treated:
    - apply a thick layer of cream to the area to be treated, about 1.5 to 2 g of cream to an area that is 10 cm^2;
        - 1.5 to 2 g is about half of a 5 g tube;
        - a 10 cm^2 area is a little larger than the size of a two dollar coin or "toonie").
    - leave the EMLA Cream on for at least 2 hours.

You will not get any added benefit from leaving EMLA Cream on for longer than 5 hours.

DOSAGE OF EMLA CREAM ON LEG ULCERS
Talk to your healthcare professional **before** using EMLA Cream on leg ulcers.

For topical anesthesia before your leg ulcer(s) are cleansed:

- apply a thick layer of cream to the area to be treated, about 1.5 to 2 g of cream to an area that is 10 cm^2;
    - 1.5 to 2 g is about half of a 5 g tube;
    - a 10 cm^2 area is a little larger than the size of a two dollar coin or "toonie").
- use no more than 10 g (two 5 g tubes).
- leave EMLA Cream on the leg ulcer(s) for at least 30 minutes. Leaving EMLA Cream on for 60 minutes may improve the numbness you feel.
- the cleansing of the leg ulcer(s) should begin within 10 minutes after removing the cream.
- discard the tube of EMLA Cream with any remaining contents after each treatment.

DOSAGE OF EMLA CREAM ON THE GENITALS
Talk to your healthcare professional **before** using EMLA Cream on your genitals.

Apply EMLA Cream when you are with your healthcare professional because it only needs to be on your skin for 5-10 minutes before the procedure.

For needle insertion or for surgical treatment of small lesions (removal of warts or a biopsy):

- use half of a 5 g tube (2 g) on the area to be treated. You may need to put the cream on a few areas.

You do not need an airtight dressing when using EMLA Cream on the genitals. Your healthcare professional should begin the surgical procedure immediately after removing the cream.

<u>Children</u>

- Observe your child closely during and after use of topical anesthetics. Children are at greater risk than adults for serious side effects, especially infants under 3 months of age.
- When using EMLA Cream for your child's pain relief, remember it is also very important to provide comfort and emotional support.
- In children, EMLA Cream should only be applied to healthy, unbroken skin.

Infants Under the Age of 3 Months:

- Use only for infants under the age of 3 months if instructed by a healthcare professional.

- Apply up to 1 g of cream on a skin area not larger than 10 cm^2 (a little larger than the size of a two dollar coin or "toonie").
- Leave on for 1 hour. Do NOT leave EMLA Cream on the skin for longer than 1 hour.

Infants Between 3 and 12 Months of Age:

- Apply up to 2 g of cream on a total skin area not larger than 20 cm^2 (a little larger than the size of a credit card).
- Leave on for at least 1 hour. Do not leave on the skin for more than 4 hours.

Children Between 1-6 Years:

- Apply up to 10 g of cream on a total skin area not larger than 100 cm^2 (a little larger than the size of two credit cards).
- Leave on for at least 1 hour. Do not leave on the skin for more than 5 hours.

Children Between 7-12 Years:

- Apply up to 20 g of cream on a total skin area not larger than 200 cm^2 (a little larger than a standard postcard).
- Leave on for at least 1 hour. Do not leave on the skin for more than 5 hours.

Overdose:

If you think you, or a person you are caring for, have taken too much EMLA Cream, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using EMLA Cream?

These are not all the possible side effects you may feel when taking EMLA Cream. If you experience any side effects not listed here, tell your healthcare professional.

Your skin where EMLA Cream was applied may stay numb for up to several hours after you take the cream off. Be careful to avoid hurting your skin until your skin isn't numb anymore. This includes scratching, rubbing or exposing your skin to extreme hot or cold temperatures.

The following side effects can happen to the skin where the cream was applied:

- whitening or redness
- slight swelling or puffiness
- initial burning or itching
- tingling of the skin, warmth
- small red dots or purple spots

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Methaemoglobinaemia: brownish or greyish skin especially around lips and nails.			✓
Eye irritation: if EMLA Cream enters the eye, immediately rinse the eye in water.			✓
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
VERY RARE			
Central nervous system toxicity: seizures, dizziness, fainting, feeling drowsy, loss of consciousness.			✓
Cardiovascular collapse: severe chest pain and pressure, nausea, vomiting, shortness of breath, trouble breathing, stopping breathing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep EMLA Cream well out of the reach and sight of children.
- Store EMLA Cream at room temperature (15-30°C). Protect from freezing.
- Do not use EMLA Cream after the expiry date on the tube or after 30 days of opening the tube. Remember to return any unused EMLA Cream to your pharmacist.

If you want more information about EMLA Cream:

- Talk to your healthcare professional
  - Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.aspenpharma.ca, or by calling 1-844-330-1213.

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