

## **PRODUCT MONOGRAPH**

EMLA<sup>®</sup> Cream

EMLA<sup>®</sup> Patch

Lidocaine 2.5% and Prilocaine 2.5%

Cream and Patch

Topical Anesthetic for Dermal Analgesia

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## EMLA<sup>®</sup> Cream

## EMLA<sup>®</sup> Patch

Lidocaine 2.5% and Prilocaine 2.5%

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Topical	Cream, 2.5% + 2.5%	carboxypolymethylene, polyoxyethylene hydrogenated castor oil, sodium hydroxide to adjust pH to 8.7-9.7, purified water Patch Components: cellulose and cotton disc, polyethylene foam with acrylate adhesive, polyamide/aluminium/plastic and polypropylene/aluminium/plastic laminates
Topical	Patch, 2.5% + 2.5%	

#### INDICATIONS AND CLINICAL USE

EMLA Cream (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 (see Part II: CLINICAL TRIALS; Topical Analgesia in Pediatrics; Vaccination): MMR, DTPP; *Haemophilus influenzae* b and Hepatitis B. 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.

**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 WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS).**

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 cauterly, 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 (see Part II: CLINICAL TRIALS; Topical Analgesia in Pediatrics; Vaccination): MMR, DTP; *Haemophilus influenzae b* and Hepatitis B. Since the effect of EMLA on the immune response to any other vaccine is unknown, it cannot be recommended for use with other vaccines.

## **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 (see DOSAGE FORMS, COMPOSITION AND PACKAGING);
- patients with congenital or idiopathic methemoglobinemia;
- 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 DRUG INTERACTIONS);
- preterm infants (defined as gestational age less than 37 weeks).

## **WARNINGS AND PRECAUTIONS**

### **General**

**Serious and life-threatening systemic adverse events, including methemoglobinemia, 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 ADVERSE REACTIONS; 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 to limit the dose and area of application (see 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 DOSAGE AND ADMINISTRATION). 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., methemoglobinemia).**

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 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.

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 tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2,6-xylylidine, showed weak evidence of activity in some genotoxicity tests. A chronic oral toxicity study of the metabolite 2,6-xylylidine (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-xylylidine for 2 years. The lowest tumor-inducing dose tested in animals (135 mg/kg) corresponds to approximately 60 times the amount of 2,6-xylylidine 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-xylylidine. Based on a yearly exposure (once daily dosing with 2,6-xylylidine 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.

## **Hepatic**

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 DOSAGE AND ADMINISTRATION).

## **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 ACTION AND CLINICAL PHARMACOLOGY). 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 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. A shorter application time should be used (see ACTION AND CLINICAL PHARMACOLOGY). There have been two reports of purpura at the application site after 60 minutes. After a repeated application of 30 minutes in one of these patients, no reaction was seen. There are not sufficient data available to characterize absorption or local reactions, nor to permit dosing recommendations.

### **Vaccination**

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.

### **Special Populations**

EMLA is contraindicated for patients with congenital or idiopathic methemoglobinemia and for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs (see also CONTRAINDICATIONS). Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methemoglobinemia.

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 also DOSAGE AND ADMINISTRATION).

**Pregnant Women:** 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.

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

**Nursing Women:** 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.

**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., methemoglobinemia).**

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 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 DOSAGE AND ADMINISTRATION, Table 2).

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 levels is commonly observed up to 12 hours after an application of EMLA.

EMLA should not be used:

- in patients with congenital or idiopathic methemoglobinemia;
- in infants who require treatment with methemoglobin-inducing agents such as sulfonamides, and are 12 months of age or younger (see also CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ADVERSE REACTIONS, Part II: CLINICAL TRIALS and DETAILED PHARMACOLOGY);
- in preterm infants (defined as a gestational age less than 37 weeks).

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

**Geriatrics:** 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 ACTION AND CLINICAL PHARMACOLOGY)

## ADVERSE REACTIONS

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

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<b>Adverse Reactions</b>	
<b>Intact Skin (for all age groups)</b>	
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 conjunction with methemoglobin-inducing agents (e.g., sulfonamides) (see 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 <sup>†</sup> .
<b>Genital Mucosa</b>	
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.

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## Adverse Reactions

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### 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.

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<sup>†</sup>During postmarketing experience serious and life threatening systemic adverse events, including methemoglobinemia, 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).

## DRUG INTERACTIONS

### Overview

Lidocaine is mainly metabolized in the liver to its two major pharmacologically active metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (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 methemoglobinemia (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ADVERSE REACTIONS, Part II: CLINICAL TRIALS).

### Drug-Drug Interactions

#### Local anesthetics and agents structurally related to amide-type local anesthetics

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 (e.g. antiarrhythmics such as mexiletine), as the toxic effects are additive.

## Antiarrhythmic Drugs

### *Class I Antiarrhythmic drugs*

Class I antiarrhythmic drugs (such as mexiletine) should be used with caution since toxic effects are additive and potentially synergistic. (see CONTRAINDICATIONS regarding infants, ADVERSE REACTIONS, and OVERDOSAGE).

### *Class III Antiarrhythmic drugs*

Caution is advised when using Class III antiarrhythmic drugs concomitantly with EMLA due to potential pharmacodynamic or pharmacokinetic interactions, or both. A drug interaction study has shown that the plasma concentration of lidocaine may be increased following administration of a therapeutic dose of intravenous lidocaine to patients treated with amiodarone (n=6). Case reports have described symptoms of lidocaine toxicity in patients treated concomitantly with lidocaine and amiodarone. Patients treated with Class III antiarrhythmic drugs (e.g. amiodarone) should be kept under close surveillance and ECG monitoring should be considered, since cardiac effects of these drugs and EMLA Cream may be additive.

### Drugs that reduce the clearance of lidocaine

Drugs that reduce the clearance of lidocaine (e.g., cimetidine or beta-blockers) may 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.

## **Methemoglobinemia**

Prilocaine, a component of EMLA, accentuates the formation of methemoglobin (MetHb) by a mechanism involving metabolism of prilocaine to o-toluidine and subsequent oxidation of hemoglobin to MetHb. The *in vivo* reduction of MetHb back to O<sub>2</sub>Hb is dependent on the presence of MetHb reductase.

In patients treated concomitantly with EMLA and other methemoglobin-inducing agents including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapson, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine, EMLA may induce the formation of methemoglobin and result in overt clinical signs of methemoglobinemia (see CONTRAINDICATIONS and OVERDOSAGE).

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.

## **Drug-Food Interactions**

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

## **Drug-Herb Interactions**

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

## **Drug-Laboratory Tests Interactions**

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

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Conditions where dosing may require adjustment:

- in acutely ill, debilitated or elderly patients, 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)
- in patients who are administered other local anesthetics or amide type local anesthetics (see DRUG INTERACTIONS)
- in debilitated patients, or those with impaired elimination, smaller application areas are recommended to avoid toxicity. Decreased duration of application is not recommended as this may decrease the analgesic effect

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., methemoglobinemia)

### **Recommended Dose and Dosage Adjustment**

**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 CONTRAINDICATIONS, ADVERSE REACTIONS, OVERDOSAGE).**

**Do not exceed dosages outlined in the tables below.**

At each recommended dose (g cream / cm<sup>2</sup> 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).

Tables 1 and 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.

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

## EMLA Cream

**Table 1 ADULTS: Recommended Dosage of EMLA cream According to Body Surface, and Procedure<sup>a</sup>**

Surface	Procedure	Cream Application
<b>Intact Skin</b>	Minor procedures, e.g., needle insertion, surgical treatment of localized lesions, and laser treatment <sup>a, b</sup> .	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 <sup>2</sup> . Approx. 2 g (1/2 of 5 g tube) for a minimum of 1 hour. Maximum 5-hour application <sup>c</sup> .
	Dermal procedures performed on larger areas, in a hospital setting, e.g., split-skin grafting <sup>d</sup> .	1.5 - 2 g/10 cm <sup>2</sup> , up to a total of 60 g. Maximum recommended treated area: 400 cm <sup>2(d)</sup> . Minimum application time: 2 hours. Maximum application time: 5 hours <sup>c</sup> .
<b>Genital Mucosa</b>	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 <sup>e</sup> . Occlusion is not necessary. Commence procedure immediately after removal of cream.
<b>Leg Ulcers</b>	Mechanical cleansing/debridement of leg ulcers <sup>f</sup>	Approx. 1-2 g/10cm <sup>2</sup> area, up to a total of 10 g. 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<sup>2</sup> (n=232). A small number of patients in these clinical trials had EMLA applied to treatment areas > 400 cm<sup>2</sup> (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
<b>In general, approx. 1 g/10 cm<sup>2</sup> area for 1 hour under a dressing to minimize the potential for the child to accidental spread the cream outside of the treatment area. Remove the dressing and clean the area of any excess cream thoroughly prior to the procedure.</b>	
Neonates 0 up to 3 months or <5 kg <sup>a, b</sup> (minimal gestational age is 37 weeks)	0.5 to 1.0 g, and up to 10 cm <sup>2</sup> area for approximately 1 hour. Standard dose = 1.0 g. Maximum 1-hour application <sup>c, d</sup> . No more than one application site at a time. The safety of repeated dosing has not been established.
Infants 3 up to 12 months <sup>b</sup> and > 5 kg	Up to 2 g and 20 cm <sup>2</sup> for approximately 1 hour <sup>e</sup> . Maximum 4-hour application.
Children 1-6 years and > 10 kg	Up to 10 g and 100 cm <sup>2</sup> for a minimum of 1 hour. Maximum 5-hour application <sup>f</sup> .
Children 7-12 years and > 20 kg	Up to 20 g and 200 cm <sup>2</sup> for a minimum of 1 hour. Maximum 5-hour application <sup>f</sup> .

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 methemoglobinemia 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 levels has been observed after an application time of up to 4 hours on 16 cm<sup>2</sup>.
- 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<sup>2</sup>) to Inches<sup>2</sup> and to a Reference Object of Comparable Size**

cm <sup>2</sup>	inch <sup>2</sup>	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	Patch Application
Intact Skin only	Minor procedures, e.g., needle insertion.	Apply patch(es) only to selected skin area(s) <10 cm <sup>2</sup> . One or more patches applied for a minimum of 1 hour. Maximum 5-hour application <sup>a</sup> . 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	Patch Application
	Apply patch(es) only to selected skin area(s) < 10 cm <sup>2</sup> <sup>a</sup> . Remove patch and clean the area thoroughly prior to procedure.
Neonates 0 up to 3 months or <5 kg <sup>b,c</sup>	1 patch applied for approx. 1 hour. Maximum 1-hour application <sup>d</sup> . 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 <sup>c</sup> and > 5 kg	Patch applied for approx. 1 hour <sup>d</sup> . Maximum 4-hour application. No more than 2 patches applied at the same time <sup>e</sup> .
Children 1-6 years and > 10 kg	One or more patches applied for a minimum of 1 hour. Maximum 5-hour application <sup>f</sup> . 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 <sup>f</sup> . 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 methemoglobinemia 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 levels has been observed after an application time of up to 4 hours on 16 cm<sup>2</sup>.
- 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.

## **Administration**

See Part III: Consumer Information – Instructions for Application.

## **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

### **Methemoglobinemia**

Rare cases of methemoglobinemia have been reported.

Mild methemoglobinemia 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 marbling.

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

Drug-induced methemoglobinemia may occur with the use of drugs including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapson, 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 methemoglobinemia 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 methemoglobinemia (see also CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

## **Class 1 Antiarrhythmic drugs**

Class 1 antiarrhythmic drugs (such as mexiletine) should be used with caution since the toxic effects are additive and potentially synergistic.

### **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 methemoglobinemia 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. Methemoglobinemia 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 methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency because it may not be effective for these patients and may cause hemolytic anemia.

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.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action and Pharmacodynamics**

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.

EMLA may produce a transient biphasic vascular response involving initial vasoconstriction followed by vasodilation at the application site (see 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.

## **General 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.

## **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 patients, within one hour after application of 4-6 g EMLA to a 25 cm<sup>2</sup> 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. In patients with atopic dermatitis, a shorter application time should be used (see WARNINGS AND PRECAUTIONS; Skin). It should be noted, however, that dermatological procedures were not performed in the above patients. Clinical data are not available at present to permit dosage recommendations.

**Distribution and 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.

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.

**Excretion:** 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).

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 WARNINGS AND PRECAUTIONS; Geriatrics)

### **Specific Pharmacokinetics for Lidocaine and Prilocaine in EMLA products**

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 have been found to be below 1.2 µg/mL. These are below the levels associated with systemic toxicity (5 µg/mL). (For detailed plasma drug levels under the indicated uses in adults and children, see Part II: CLINICAL TRIALS; Lidocaine and Prilocaine Levels following Topical Application of EMLA).

## **STORAGE AND STABILITY**

**EMLA Cream** (lidocaine and prilocaine) in aluminium tubes should be stored at room temperature (15-30°C). Protect from freezing.

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

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **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 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<sup>2</sup>. The surface area of the entire patch is approximately 40 cm<sup>2</sup>. EMLA Patch is available in boxes of 2 or 20 single-use patches per box, 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 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

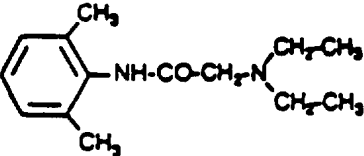
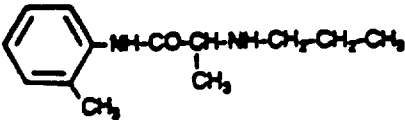
Patch Components:

Cellulose and cotton disc  
Polyethylene foam with acrylate adhesive  
Polyamide/aluminium/plastic and polypropylene/aluminium/plastic laminates

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name	lidocaine	prilocaine
Chemical name	2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide	N-(2-methylphenyl)-2-(propylamino)-propanamide
Molecular formula and molecular mass	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> O 234.3	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O 220.3
Structural formula		
Physicochemical properties		
Description	White to almost white crystalline powder	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	In water: slightly soluble In ethanol: very soluble In acetone: very soluble
Boiling point	146°C at 1 mm Hg 166°C at 3 mm Hg	156°C to 158°C at 1 mm Hg
pKa	7.9	7.9

## **CLINICAL TRIALS**

### **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 (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).

##### **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.

#### ***Topical Analgesia in Pediatrics (including neonates)***

##### **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 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 (Diphtheria-Pertussis-Tetanus-Poliovirus); *Hemophilus influenzae* b; Hepatitis B; Fluzone<sup>®</sup> and tetanus. The efficacy of EMLA in reducing the pain of any other vaccine is unknown (see 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 (NFCS), 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 methemoglobinemia.

### Vaccination

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

EMLA has been shown to effectively reduce the pain associated with vaccination in all age groups (see 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  $\geq 4$  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.

Although the two pivotal trials investigated the immune response following administration of EMLA Patch, there is reason to believe that similar immunogenicity results would be achieved using EMLA Cream under the same circumstances.

### **EMLA Patch**

For pain relief in venepuncture, EMLA patch has been shown to be efficacious and safe (see Part I: DOSAGE FORMS, COMPOSITION AND PACKAGING). There have been no observed local skin reactions of clinical significance.

### **Lidocaine and Prilocaine Plasma Levels following Topical Application of EMLA**

Plasma levels of lidocaine and prilocaine associated with systemic toxicity are approximately 5  $\mu\text{g}/\text{mL}$  for each drug. There is a large inter-subject variation in the absorption of lidocaine and prilocaine; however, in clinical trials in adults and in the pediatric population, plasma levels of both drugs remained well below toxic levels.

#### ***Studies in Adults:***

##### **Intact skin**

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  $\text{cm}^2$  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  $\mu\text{g}/\text{mL}$  for lidocaine and 0.07  $\mu\text{g}/\text{mL}$  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  $\mu\text{g}/\text{mL}$ , which is far below potentially toxic levels of 5  $\mu\text{g}/\text{mL}$ .

Following the application of approximately 150 g of EMLA cream to intact skin areas of up to 1,300  $\text{cm}^2$ , for up to 3 hours duration, the highest individual plasma levels observed were 1.1  $\mu\text{g}/\text{mL}$  lidocaine and 0.2  $\mu\text{g}/\text{mL}$  prilocaine. These plasma levels remained below the levels at which symptoms of toxicity would be expected (5  $\mu\text{g}/\text{mL}$  either agent).

Following application to the face (10 g/100 cm<sup>2</sup> 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.

#### Split-Skin Grafting

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

Following a 10-minute application of 10 g EMLA cream to vaginal mucosa, maximum mean plasma concentrations of lidocaine and prilocaine were 0.18 µg/mL and 0.15 µg/mL, respectively. Individual maximum plasma concentrations obtained for lidocaine and prilocaine ranged from 0.15 to 0.23 µg/mL and 0.12 to 0.18 µg/mL, respectively, and were reached in 20-45 minutes.

#### Leg Ulcers

Following the application of 5 to 10 g of EMLA to leg ulcers 15 to 64 cm<sup>2</sup> 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<sup>2</sup> to leg ulcers 50 to 100 cm<sup>2</sup>, 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.

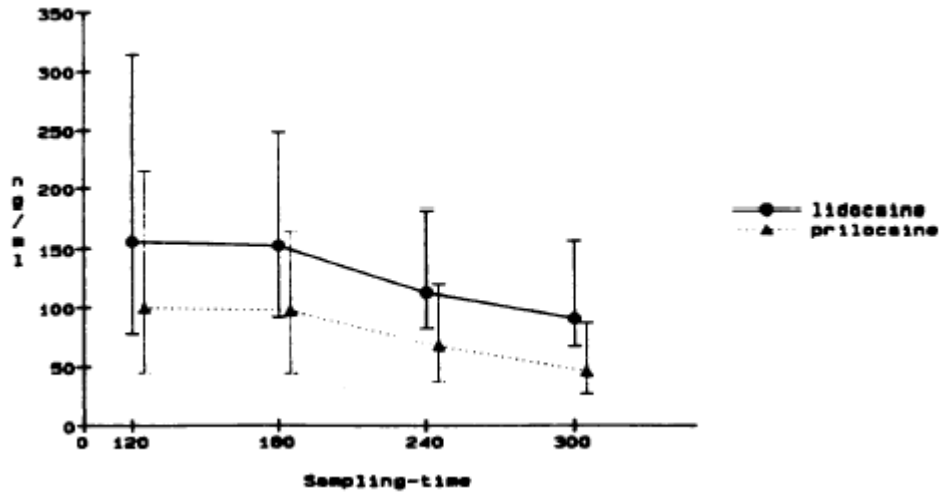
In clinical studies, the repeated use of EMLA cream prior to the cleansing of leg ulcers has been evaluated in 88 patients. Application of 1 to 10 g/10 cm<sup>2</sup> for 30-60 minutes, up to 15 times within a 1 - 2 month period, resulted in no apparent loss of analgesic effect or increase in local reactions. The maximum observed plasma levels for lidocaine, monoglycinylylidide and 2,6-xylylidine 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.

#### ***Studies in Pediatrics:***

##### 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 (see CLINICAL TRIALS; Topical Analgesia in Pediatrics).

**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 <sup>2</sup> )	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 <sup>2</sup>	1	0.135	0.107	4-6
Infants (3-12 mos)	22	2 g/16 cm <sup>2</sup>	4	0.155	0.131	4
Children (2-3 years)	10	100 g/100 cm <sup>2</sup>	2	0.315	0.215	2
Children (6-8 years)	10	10-16 g/100-160 cm <sup>2</sup>	2	0.299	0.110	2-2.5

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

***Studies in Neonates:***

Methemoglobinemia (see Part I: CONTRAINDICATIONS and OVERDOSAGE)

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 methemoglobinemia, a condition in which hemoglobin cannot bind and deliver oxygen normally.

A metabolite of prilocaine, o-toluidine, is known to induce methemoglobinemia. 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 methemoglobinemia 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 methemoglobinemia is typically not needed unless metHb concentrations are nearing 25%. (see Part I: OVERDOSAGE)

MetHb, Prilocaine and Lidocaine Plasma Levels

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.

### ***Studies in 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 Part I: WARNINGS AND PRECAUTIONS; Geriatrics).

## **DETAILED PHARMACOLOGY**

### **Animal Studies**

Topical application of a eutectic mixture of lidocaine and prilocaine results in percutaneous local anesthesia as demonstrated by studies on the shaven, depilated backs of guinea pigs. After a 60-minute application time, the animals were sacrificed and the skin of the test area dissected and examined. Higher concentrations of lidocaine and prilocaine were found when the agents were applied together as a eutectic mixture (EMLA) than when either agent was applied alone. The results also indicated that both agents are absorbed more rapidly by the skin when applied as EMLA (lidocaine and prilocaine) than alone.

When absorbed, both lidocaine and prilocaine are partly converted to ionic forms because of the pH of the tissue fluids and the pK<sub>a</sub> of the substances.

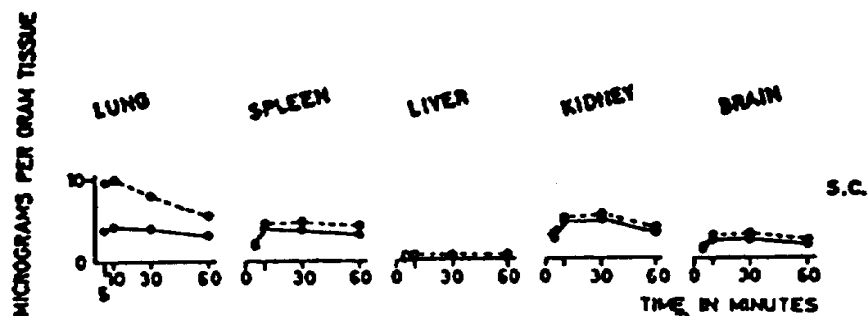
The plasma levels of the two agents were measured in the rabbit during a 24-hour application of 10 g of EMLA cream 43% (i.e., 4300 mg, dermally) on 200 cm<sup>2</sup> of skin area (about 10% of the total body area). Plasma levels were also measured at 1, 6, 24, 25, 30 and 49 hours after removal of the cream.

The results showed that the plasma level of lidocaine was higher than that of prilocaine, which is consistent with the distribution properties. The levels for both substances increased rapidly during the first few hours of application, then reached a steady state level which was relatively constant for the rest of the application time. The initial phase of elimination after removal of the emulsion cream was more rapid than the later phase for both the substances. Twenty-five hours after removal of the cream, the measured levels of lidocaine and prilocaine were 28% and 7.5%, respectively, of the levels recorded at the time of removal.

The tissue distribution of a subcutaneously-injected mixture of 5 mg/kg each of <sup>14</sup>C-prilocaine-HCl and <sup>3</sup>H-lidocaine-HCl in the rat has also been studied. The general pattern

of distribution was the same for both drugs, although the concentrations of prilocaine tended to be higher in all the tissues studied (see Figure 2).

**Figure 2** Tissue Distribution of Lidocaine and Prilocaine in Rats after Subcutaneous Injection of a Mixture of 5 mg/kg  $^{14}\text{C}$ -prilocaine plus 5 mg/kg  $^3\text{H}$ -lidocaine. O-----O = prilocaine: •-----• = lidocaine.



The excretion of lidocaine has also been studied in a variety of animal species. Following the administration of radioactive lidocaine, it was found that the majority of the administered radioactivity was recovered in the urine, almost exclusively as lidocaine metabolites.

The elimination of prilocaine in the urine and feces was investigated in rats after an intraperitoneal injection of 20 mg/kg  $^{14}\text{C}$ -labelled compound. Approximately 25% of the injected radioactivity was recovered in the urine after 6 hours; the majority of the excretion in the urine consisted of prilocaine metabolites. The feces contained no detectable amounts of radioactivity.

## TOXICOLOGY

### Acute 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  $\text{LD}_{50}$  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 Species	Strain	Sex	Number	Route of Administration	Test Compound	LD <sub>50</sub> (mg/kg) Day 1, Day 14
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 Administration

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<sup>2</sup> 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.

### Chronic Toxicity

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.

### **Teratogenicity**

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.

### **Mutagenicity**

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).

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.

### **Eye Irritation Test**

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.

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**EMLA<sup>®</sup> Patch**  
lidocaine 2.5% and prilocaine 2.5% Patch

### **PART III: CONSUMER INFORMATION**

This leaflet is part III of a three-part "Product Monograph" published when EMLA<sup>®</sup> Patch was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EMLA<sup>®</sup> Patch. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet to refer to until you have used up all your EMLA Patches.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- EMLA Patch should only be used according to the section **WHAT THE MEDICATION IS USED FOR** because maximum safe doses for other uses are not known.
- If your doctor has not explained how to use EMLA Patch, make sure you read and understand the section, **PROPER USE OF THIS MEDICATION**. Follow the instructions. Ask your doctor or pharmacist to explain the proper use of EMLA Patch if you do not understand these instructions. Serious and life threatening side effects have occurred when EMLA Cream was not used properly.

#### **WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT EMLA**

EMLA contains 2.5% lidocaine and 2.5% prilocaine.

Be careful to apply no more than the maximum recommended dose of EMLA Patch. Serious side effects from applying too much EMLA Patch can include:

- drowsiness,
- numbness of the tongue,
- brownish or greyish skin especially around lips and nails,
- light-headedness,
- confusion,
- headache,
- sight or hearing problems,
- difficulty breathing,
- vomiting, dizziness,
- weakness,

- unusually slow heart beat,
- fainting,
- nervousness,
- unusual sweating,
- trembling
- seizures

Get medical help right away, if you experience any of these side effects.

#### **ABOUT THIS MEDICATION**

##### **WHAT THE MEDICATION IS USED FOR:**

EMLA Patch is used to create a temporary loss of feeling or numbness of small areas of skin (slightly larger than a two dollar coin or "toonie") and can be used:

- prior to getting a needle or having blood taken, and only on healthy, unbroken skin;
- prior to vaccination with only the following vaccines: MMR (Measles-Mumps-Rubella), DPTP (Diphtheria-Pertussis-Tetanus-Poliiovirus), *Haemophilus influenzae b* or Hepatitis B. Since the effect of EMLA on the immune response to any other vaccine is unknown, it cannot be recommended for use with any other vaccine.

##### **WHAT IT DOES:**

EMLA is the brand name for a topical anesthetic that contains the drugs lidocaine and prilocaine. Topical anesthetics are used to cause a temporary loss of feeling or numbness of the skin at the area where it is applied.

##### **WHEN IT SHOULD NOT BE USED:**

- if you/your child have methemoglobinemia (a blood disorder);
- on infants who require methemoglobin-inducing agents (e.g., sulfonamides), and are 12 months of age or younger;
- if you are allergic to lidocaine, prilocaine, any other "-caine" type anesthetics, or any of the non-medicinal ingredients in the product (see **WHAT THE NONMEDICINAL INGREDIENTS ARE** section below);
- on infants less than 3 months of age, unless instructed by your doctor.
- for procedures requiring large amounts of EMLA over a large body area that are not conducted in a hospital.

##### **WHAT THE MEDICINAL INGREDIENT IS:**

lidocaine 2.5% and prilocaine 2.5%

##### **WHAT THE NONMEDICINAL INGREDIENTS ARE:**

EMLA Patch is composed of a tan-coloured adhesive tape with a round white pad in the centre that contains EMLA. The adhesive tape is protected with a peel-off backing which is removed before the patch is applied.

EMLA Patch also contains carboxypolymethylene, polyoxyethylene hydrogenated castor oil, and sodium hydroxide. The patch adhesive is made from acrylate. The patch does not contain latex.

**WHAT DOSAGE FORMS IT COMES IN:**

EMLA<sup>®</sup> Patch: 1 g patches

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

**EMLA Patch is for use on healthy, unbroken skin. Do not apply to open wounds, nor to burns or rashes or other skin conditions, including diaper rash.**

BEFORE you use EMLA Patch talk to your doctor or pharmacist if:

- if you/your child have glucose- 6-phosphate dehydrogenase deficiency;
- if you/your child have ever had a bad, unusual or allergic reaction to lidocaine or prilocaine, also available under brand names such as Xylocaine<sup>®</sup> (lidocaine) and Citanest<sup>®</sup> (prilocaine);
- if you think you/your child might be sensitive or allergic to other ingredients of the patch (see WHAT THE NONMEDICINAL INGREDIENTS ARE);
- if there is an infection, skin rash or cut at, or near, the area where you want to apply EMLA Patch;
- if you/your child have dermatitis or any other skin problems or diseases;
- if you/your child have severe kidney or liver disease (see PROPER USE OF THIS MEDICATION);
- if you are pregnant, trying to become pregnant or are breastfeeding.

**INTERACTIONS WITH THIS MEDICATION**

Tell your doctor or pharmacist about any other drugs you take, or have recently taken including the ones you can buy without a prescription, including:

- antiarrhythmic drugs for heart problems (e.g. mexilitine, amiodarone);
- other anesthetics;
- other drugs which may trigger methemoglobin formation, 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.

**PROPER USE OF THIS MEDICATION**

**USUAL DOSE:**

Do not apply the EMLA Patch to infants under 3 months of age unless a doctor tells you to do so. Infants under 3 months of age are at a higher risk than older children for methemoglobinemia. This is a condition in which there is not enough oxygen in the blood, and it can be caused by an overdose of EMLA.

If your doctor tells you to use EMLA Patch, follow your doctor's instructions for use. In any other situation, follow the directions below.

Do not put EMLA Patch near the eyes, as it may cause some irritation. If you accidentally get EMLA in the eye, rinse it well with lukewarm water and protect it until sensation returns.

Do not apply EMLA Patch inside the ear. 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 an EMLA Patch is accidentally swallowed, call your doctor.

Do not re-use EMLA Patch.

The numbing effect of EMLA starts working about 1 hour after it is applied. You may still feel pressure and touch in the area where you apply EMLA. 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.

**Conditions where adjustments in dose may be required:**

- elderly patients
- acutely ill patients
- patients with severe liver disease
- patients with severe kidney disease
- patients also treated with other anesthetics or certain antiarrhythmic drugs (e.g. mexilitine, amiodarone)

EMLA should be used with caution in these patients, who may be more sensitive to the effects of lidocaine and prilocaine.

**Adults**

**Be careful not to apply more EMLA Patch or replace it more frequently than the doctor recommended.**

Serious and life threatening side effects have occurred when EMLA Cream was not used properly and more than the recommended amounts were applied.

EMLA Patch must be applied for at least 1 hour before the procedure. You will not get any added benefit from leaving EMLA Patch on for longer than 5 hours.

**Pediatrics**

**Be careful not to apply more EMLA Patch or replace it more frequently than the doctor recommended.**

**Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious side effects, such as methemoglobinemia (a blood disorder that causes the skin, especially around lips and nails, to turn brownish or greyish). See also SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM.**

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

**Infants Under 3 Months (ONLY IF INSTRUCTED BY A DOCTOR):**

Do not use more than one EMLA Patch at the same time. Leave the patch on for 1 hour. 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:**

Do not use more than two EMLA Patches at the same time. Leave the patch on for at least 1 hour. Do not leave EMLA Patch on the skin for more than 4 hours.

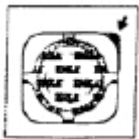
**Children Between 1-6 Years:**

Apply one or more patches to the skin area selected for 1 hour. Do not leave on the skin for more than 5 hours. Apply up to 10 patches.

**Children Between 7-12 Years:**

Apply one or more patches to the skin area selected for at least 1 hour. Do not leave on the skin for more than 5 hours. Apply up to 20 patches.

**INSTRUCTIONS FOR APPLICATION OF 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 EMLA.



3. Apply EMLA patch so that the white, round pad containing EMLA 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 that EMLA 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. Care should be taken that the patch does not become detached during the 1 hour 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 doctor, you should leave it on for the doctor to remove, unless instructed otherwise.

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

**OVERDOSE:**

In case of EMLA overdose or if you think you, or anyone else, are experiencing any of the side effects described below or methemoglobinemia, contact your doctor, hospital emergency department or regional Poison Control Centre immediately. You may require medical attention.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like any medication, EMLA Patch may result in side effects in some people.

The skin to which EMLA Patch is applied may stay numb for up to several hours after the cream is removed. For this reason, you should be careful to avoid accidental injury to the treated area, such as scratching, rubbing or exposure to extreme hot or cold temperatures, until complete sensation returns.

Mild side effects that are common with use of EMLA are whitening or redness of the skin, slight puffiness, and initial burning or itching on the skin where EMLA is applied. These are normal reactions and will disappear without any treatment.

Allergic reactions to the active ingredients have been seen but are rare.

Medicines affect different people in different ways. Just because side effects have occurred in some patients, does not mean that you will get them. *If any side effects bother you, or if you experience any unusual effects while you are using EMLA, stop using it. Talk to your doctor or pharmacist as soon as possible.*

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
<b>Rare</b>	Methemoglobinemia [reduced oxygen to body tissues causing brownish or greyish skin especially around lips and nails]			X
<b>Rare</b>	Eye irritation			X*
<b>Rare</b>	Allergic reaction			X

\*If EMLA Patch accidentally enters the eye, immediately rinse the eye in water or sodium chloride solution and protect the eye until sensation returns. Contact your doctor or pharmacist.

*This is not a complete list of side effects. For any unexpected effects while taking EMLA Patch, contact your doctor or pharmacist.*

EMLA Patch can cause serious side effects if too much is applied. These include drowsiness, numbness of the tongue, discoloured skin, light-headedness, confusion, headache, sight or hearing problems, difficulty breathing, vomiting, dizziness, weakness, unusually slow heart beat, fainting, nervousness, unusual sweating, trembling or seizures. Stop taking the drug and seek immediate emergency help if you experience any of these side effects. Irritation may occur when eyes are accidentally exposed to EMLA.

If someone using EMLA shows these signs, or any other sign of being unwell, they should seek immediate medical attention.

Methemoglobinemia

EMLA Patch, in extremely rare cases, can affect the level of oxygen that the blood carries, resulting in an increase in the methemoglobin level in your blood. This condition, known as methemoglobinemia, causes the colour of the skin to become brownish or greyish, especially around the lips, fingernails and toenails. If you see this happening, go to the nearest hospital right away.

**HOW TO STORE IT**

Keep EMLA Patch well out of the reach of children. Store EMLA Patch at room temperature. Protect from freezing.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)  
 Call toll-free at: 1-866-234-2345  
 Complete a Canada Vigilance Reporting Form and:  
 -Fax toll-free to: 1-866-678-6789 or,  
 -Mail to: Canada Vigilance Program  
 Health Canada  
 Postal Locator 0701C  
 Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

**NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.**

**MORE INFORMATION**

**Important Note: This leaflet alerts you to some of the times you should call your doctor while using EMLA Patch. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor with any questions or concerns you have about using EMLA Patch.**

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: [www.astrazeneca.ca](http://www.astrazeneca.ca) under Patients with Prescriptions, or by contacting the sponsor, AstraZeneca Canada Inc. at:  
 Customer Inquiries – 1(800) 668-6000,  
 Renseignements – 1(800) 461-3787.

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**EMLA<sup>®</sup> Cream**  
lidocaine 2.5% and prilocaine 2.5% Cream

**PART III:  
CONSUMER INFORMATION**

This leaflet is part III of a three-part "Product Monograph" published when EMLA<sup>®</sup> Cream was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EMLA<sup>®</sup> Cream. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet to refer to until you have used up all your EMLA Cream.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- EMLA Cream should only be used according to the section **WHAT THE MEDICATION IS USED FOR** because maximum safe doses for other uses are not known. Applying EMLA Cream on large areas of skin can result in a medical emergency.
- If your doctor has not explained how to use EMLA Cream, make sure you read and understand the section, **PROPER USE OF THIS MEDICATION**. Follow the instructions. Ask your doctor or pharmacist to explain the proper use of EMLA Cream if you do not understand these instructions. Serious and life threatening side effects have occurred when EMLA Cream was not used properly.

**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT EMLA**

EMLA contains 2.5% lidocaine and 2.5% prilocaine.

**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 used on large areas of skin for topical analgesia during cosmetic procedures. Serious side effects from applying too much EMLA Cream can include:**

- drowsiness,
- numbness of the tongue,
- brownish or greyish skin especially around lips and nails,
- light-headedness,
- confusion,
- headache,

- sight or hearing problems,
- difficulty breathing,
- vomiting, dizziness,
- weakness,
- unusually slow heart beat,
- fainting,
- nervousness,
- unusual sweating,
- trembling
- seizures

Get medical help right away, if you experience any of these side effects.

**ABOUT THIS MEDICATION**

**WHAT THE MEDICATION IS USED FOR:**

EMLA Cream is used to create a temporary loss of feeling or numbness of the skin, and can be used:

- on healthy, unbroken skin before minor skin surgery, or when getting a needle or having blood taken;
- prior to vaccination with only the following vaccines: MMR (Measles-Mumps-Rubella), DPTP (Diphtheria-Pertussis-Tetanus-Poliovirus), *Haemophilus influenzae* b or Hepatitis B;
- on the genital mucosa;
- for the cleansing of leg ulcers.

For best results talk to your doctor before using the cream on the genital mucosa or for leg ulcers.

**WHAT IT DOES:**

EMLA is the brand name for a topical anesthetic that contains the drugs lidocaine and prilocaine. Topical anesthetics are used to cause a temporary loss of feeling or numbness of the skin at the area where it is applied.

**WHEN IT SHOULD NOT BE USED:**

- if you/your child have methemoglobinemia (a blood disorder);
- on infants who required methemoglobin-inducing agents (e.g., sulfonamides) and are 12 months of age or younger;
- if you/your child are allergic to lidocaine, prilocaine, any other "-caine" type anesthetics, or any of the non-medicinal ingredients in the product (see **WHAT THE NONMEDICINAL INGREDIENTS ARE** section below);
- on infants less than 3 months of age, unless instructed by your doctor.
- for procedures requiring large amounts of EMLA over a large body area that are not conducted in a hospital.

**WHAT THE MEDICINAL INGREDIENT IS:**

lidocaine 2.5% and prilocaine 2.5%

**WHAT THE NONMEDICINAL INGREDIENTS ARE:**

EMLA Cream also contains carboxypolymethylene, polyoxyethylene hydrogenated castor oil, and sodium hydroxide.

Tegaderm™ dressings contain polyether polyurethane films, acrylate adhesives and paper liners. These dressings are hypoallergenic and do not contain latex. (Tegaderm™ dressings are supplied with the 5 g EMLA Cream tube only).

**WHAT DOSAGE FORMS IT COMES IN:**

EMLA® Cream: 5 g and 30 g tubes

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

**EMLA Cream is for use on healthy, unbroken skin. Do not apply to open wounds, nor to burns or rashes or other skin conditions, including diaper rash.**

BEFORE you use EMLA Cream talk to your doctor or pharmacist if:

- if you/your child have glucose-6-phosphate dehydrogenase deficiency;
- if you/your child 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);
- if you think you/your child may be sensitive or allergic to other ingredients of the cream or Tegaderm™ dressing (see WHAT THE NONMEDICINAL INGREDIENTS ARE);
- if there is an infection, skin rash or cut at, or near, the area where you want to apply EMLA Cream;
- if you/your child have dermatitis or any other skin problems or diseases;
- if you/your child have severe kidney or liver disease (see PROPER USE OF THIS MEDICATION);
- if you are pregnant, trying to become pregnant or are breastfeeding;
- if you would like to use EMLA Cream prior to treatment of a leg ulcer(s);
- if you would like to use EMLA Cream on the genital area of children.

**INTERACTIONS WITH THIS MEDICATION**

Tell your doctor or pharmacist about any other drugs you take or have recently taken, including the ones you can buy without a prescription, including:

- antiarrhythmic drugs for heart problems (e.g. mexilitine, amiodarone);
- other anesthetics;

- other drugs which may trigger methemoglobin formation, 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.

**PROPER USE OF THIS MEDICATION**

**USUAL DOSE:**

If your doctor tells you to use EMLA Cream, follow your doctor's instructions for use. In any other situation, follow the directions below.

Do not put EMLA Cream near the eyes, as it may cause some irritation. If you accidentally get EMLA in the eye, rinse it well with lukewarm water and protect it until sensation returns.

Do not apply EMLA Cream inside the ear. Do not put EMLA Cream in the mouth, or swallow it. If EMLA Cream is accidentally swallowed, call your doctor.

Do not re-use EMLA Cream or dressings.

The numbing effect of EMLA starts working about 1 hour after it is applied. You may still feel pressure and touch in the area where you apply EMLA. 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.

**Conditions where adjustments in dose may be required:**

- elderly patients
- acutely ill patients
- patients with severe liver disease
- patients with severe kidney disease
- patients also treated with other anesthetics or certain antiarrhythmic drugs (e.g. mexilitine, amiodarone)

EMLA should be used with caution in these patients, who may be more sensitive to the effects of lidocaine and prilocaine.

**Adults**

**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 used on large areas of skin for topical analgesia during cosmetic procedures.**

**DOSAGE OF EMLA CREAM ON HEALTHY SKIN**

For minor procedures on skin such as surgical treatment of lesions 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". After covering EMLA Cream with an air-tight dressing, leave on for at least 1 hour. 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.

Your doctor may use EMLA Cream on larger areas for such procedures as split-skin grafting. If you are instructed by the doctor to apply EMLA Cream yourself for this procedure, apply a thick layer of cream to the area to be treated (about 1.5 to 2 g/10 cm<sup>2</sup>; 1.5 to 2 g is about half of a 5 g tube; a 10 cm<sup>2</sup> area is a little larger than the size of a two dollar coin or "toonie"). Make sure your doctor has clearly explained the size of the area to be treated. 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.

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

#### **DOSAGE OF EMLA CREAM ON LEG ULCERS**

Talk to your doctor **before** using EMLA Cream on leg ulcers.

For topical anesthesia before cleansing of leg ulcer(s), apply a thick layer of EMLA Cream over the leg ulcer(s), about 1 to 2 g/10 cm<sup>2</sup> (a little larger than the size of a two dollar coin or "toonie"). Use no more than 10 g (two 5 g tubes).

After covering EMLA Cream with an air-tight dressing, leave on the leg ulcer for at least 30 minutes. Leaving EMLA Cream on for 60 minutes may improve the anesthesia. The cleansing of the leg ulcer should begin within 10 minutes after removing the cream.

#### **DOSAGE OF EMLA CREAM ON GENITAL MUCOSA**

Talk to your doctor **before** using EMLA Cream on the genital mucosa. For best results, do not apply EMLA Cream on the genital mucosa until you are with your doctor.

For needle insertion, use half of a 5 g tube (2 g) at the selected site before the procedure.

For the surgical treatment of small lesions, such as the removal of genital warts or when having a biopsy, use about half of a 5 g tube (2 g) per lesion 5 to 10 minutes before the procedure.

You do not need an airtight dressing when using EMLA Cream on the genital mucosa. Your doctor should begin the surgical procedure immediately after removing the cream.

#### **Pediatrics**

**Be careful to apply no more than the maximum recommended dose of EMLA Cream.**

**Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious side effects, such as methemoglobinemia (a blood disorder that causes the skin, especially around lips and nails, to turn brownish or greyish). See also SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM.**

For children under the age of 6: take care not to apply more EMLA Cream or give it more frequently than the doctor recommended. Please make sure that your child does not ingest any of the cream.

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

For minor skin procedures. 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.

In children, EMLA Cream should only be applied to healthy, unbroken skin.

Do not apply EMLA Cream to infants under 3 months of age unless a doctor tells you to do so. Infants under 3 months of age are at a higher risk than older children for methemoglobinemia. This is a condition in which there is not enough oxygen in the blood, and it can be caused by an overdose of EMLA.

#### **Neonates Under the Age of 3 Months (ONLY IF INSTRUCTED BY A DOCTOR):**

Apply up to 1 g of cream on a skin area not larger than 10 cm<sup>2</sup> (a little larger than the size of a two dollar coin or "toonie"). After covering EMLA cream with an air-tight dressing, leave on for 1 hour. **DO NOT LEAVE EMLA 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<sup>2</sup> (a little larger than the size of a credit card). After covering EMLA Cream with an air-tight dressing, 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<sup>2</sup> (a little larger than the size of two credit cards). After covering EMLA Cream with an air-tight dressing, 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<sup>2</sup> (a little larger than a standard postcard). After covering EMLA Cream with an air-tight dressing, leave on for at least 1 hour. Do not leave on the skin for more than 5 hours.

**INSTRUCTIONS FOR APPLICATION ON INTACT SKIN AND LEG ULCERS**



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.



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. 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 doctor, you should leave the dressing on for the doctor to remove, unless otherwise instructed.

**OVERDOSE:**

In case of EMLA overdose or if you think you, or anyone else, are experiencing any of the side effects described below or methemoglobinemia, contact your doctor, hospital emergency department or regional Poison Control Centre immediately. You may require medical attention.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like any medication, EMLA Cream may result in side effects in some people.

The skin to which EMLA Cream is applied may stay numb for up to several hours after the cream is removed. For this reason, you should be careful to avoid accidental injury to the treated area, such as scratching, rubbing or exposure to extreme hot or cold temperatures, until complete sensation returns.

Mild side effects that are common with use of EMLA are whitening or redness of the skin, slight puffiness, and initial burning or itching on the skin where EMLA is applied. These are normal reactions and will disappear without any treatment. Allergic reactions to the active ingredients have been seen but are rare.

Rare cases of small red dots (petechiae) at the application site have been reported, especially in children with skin problems (atopic dermatitis or mollusca).

Medicines affect different people in different ways. Just because side effects have occurred in some patients, does not mean that you will get them. *If any side effects bother you, or if you experience any unusual effects while you are using EMLA, stop using it. Talk to your doctor or pharmacist as soon as possible.*

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Rare	Methemoglobinemia [reduced oxygen to body tissues causing brownish or greyish skin especially around lips and nails]			X
Rare	Eye irritation			X*
Rare	Allergic reaction			X

\*If EMLA Cream accidentally enters the eye, immediately rinse the eye in water or sodium chloride solution and protect the eye until sensation returns. Contact your doctor or pharmacist.

***This is not a complete list of side effects. For any unexpected effects while taking EMLA Cream, contact your doctor or pharmacist.***

EMLA Cream can cause serious side effects if too much is applied. These include drowsiness, numbness of the tongue, discoloured skin, light-headedness, confusion, headache, sight or hearing problems, difficulty breathing, vomiting, dizziness, weakness, unusually slow heart beat, fainting, nervousness, unusual sweating, trembling or seizures. Stop taking the drug and seek immediate emergency help if you experience any of these side effects. Irritation may occur when eyes are accidentally exposed to EMLA.

If someone using EMLA shows these signs, or any other sign of being unwell, they should seek immediate medical attention.

**Methemoglobinemia**

EMLA Cream, in extremely rare cases, can affect the level of oxygen that the blood carries, resulting in an increase in the methemoglobin level in your blood. This condition, known as methemoglobinemia, causes the colour of the skin to become brownish or greyish, especially around the lips, fingernails, and toenails. If you see this happening, go to the nearest hospital right away.

**HOW TO STORE IT**

Keep EMLA Cream well out of the reach of children. Store EMLA Cream at room temperature. Protect from freezing.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at: 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

-Fax toll-free to: 1-866-678-6789 or,

-Mail to: Canada Vigilance Program

Health Canada

Postal Locator 0701C

Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

**MORE INFORMATION**

**Important Note: This leaflet alerts you to some of the times you should call your doctor while using EMLA Cream. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor with any questions or concerns you have about using EMLA Cream.**

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