


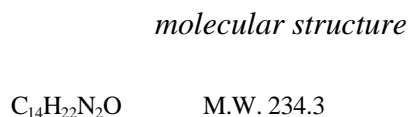
EMLA[®] (*dollop logo*)
CREAM (lidocaine 2.5%
and prilocaine 2.5%)

EMLA[®] 
Anesthetic Disc (lidocaine 2.5%
and prilocaine 2.5% cream)
Topical Adhesive System

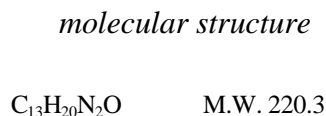
DESCRIPTION

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals. It is packaged in 5 gram and 30 gram tubes. It is also packaged in the Anesthetic Disc, which is a single-dose unit of EMLA contained within an occlusive dressing. The Anesthetic Disc is composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring. The disc contains 1 gram of EMLA emulsion, the active contact surface being approximately 10 cm². The surface area of the entire anesthetic disc is approximately 40 cm².

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4, and has the following structure:



Prilocaine is chemically designated as propanamide, N-(2-methylphenyl)-2-(propylamino), has an octanol:water partition ratio of 25 at pH 7.4, and has the following structure:



Each gram of EMLA contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), carboxypolymethylene (as a thickening agent), sodium hydroxide to adjust to a pH approximating 9, and purified water to 1 gram. EMLA contains no preservative, however it passes the USP antimicrobial effectiveness test due to the pH. The specific gravity of EMLA Cream is 1.00.

CLINICAL PHARMACOLOGY

Mechanism of Action : EMLA (lidocaine 2.5% and prilocaine 2.5%), applied to intact skin under occlusive dressing, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anesthetic agents. Both lidocaine and prilocaine stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

The onset, depth and duration of dermal analgesia on intact skin provided by EMLA depends primarily on the duration of application. To provide sufficient analgesia for clinical procedures such as intravenous catheter placement and venipuncture, EMLA should be applied under an occlusive dressing for at least 1 hour. To provide dermal analgesia for clinical procedures such as split skin graft harvesting, EMLA should be applied under occlusive dressing for at least 2 hours. Satisfactory dermal analgesia is achieved 1 hour after application, reaches maximum at 2 to 3 hours, and persists for 1 to 2 hours after removal. Absorption from the genital mucosa is more rapid and onset time is shorter (5 to 10 minutes) than after application to intact skin. After a 5 to 10 minute application of EMLA to female genital mucosa, the average duration of effective analgesia to an

argon laser stimulus (which produced a sharp, pricking pain) was 15 to 20 minutes (individual variations in the range of 5 to 45 minutes).

Dermal application of EMLA may cause a transient, local blanching followed by a transient, local redness or erythema.

Pharmacokinetics: EMLA is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% formulated as an oil in water emulsion. In this eutectic mixture, both anesthetics are liquid at room temperature (see DESCRIPTION) and the penetration and subsequent systemic absorption of both prilocaine and lidocaine are enhanced over that which would be seen if each component in crystalline form was applied separately as a 2.5% topical cream.

Absorption: The amount of lidocaine and prilocaine systemically absorbed from EMLA is directly related to both the duration of application and to the area over which it is applied. In two pharmacokinetic studies, 60 g of EMLA Cream (1.5 g lidocaine and 1.5 g prilocaine) was applied to 400 cm² of intact skin on the lateral thigh and then covered by an occlusive dressing. The subjects were then randomized such that one-half of the subjects had the occlusive dressing and residual cream removed after 3 hours, while the remainder left the dressing in place for 24 hours. The results from these studies are summarized below.

TABLE 1
Absorption of Lidocaine and Prilocaine from
EMLA Cream: Normal Volunteers (N=16)

EMLA (g)	Area (cm ²)	Time on (hrs)	Drug Content (mg)	Absorbed (mg)	Cmax (µg/mL)	Tmax (hr)
60	400	3	lidocaine 1500	54	0.12	4
			prilocaine 1500	92	0.07	4
60	400	24*	lidocaine 1500	243	0.28	10
			prilocaine 1500	503	0.14	10

* Maximum recommended duration of exposure is 4 hours.

When 60 g of EMLA Cream was applied over 400 cm² for 24 hours, peak blood levels of lidocaine are approximately 1/20 the systemic toxic level. Likewise, the maximum prilocaine level is about 1/36 the toxic level. In a pharmacokinetic study, EMLA Cream was applied to penile skin in 20 adult male patients in doses ranging from 0.5 g to 3.3 g for 15 minutes. Plasma concentrations of lidocaine and prilocaine following EMLA Cream application in this study were consistently low (2.5-16 ng/mL for lidocaine and 2.5-7 ng/mL for prilocaine). The application of EMLA to broken or inflamed skin, or to 2,000 cm² or more of skin where more of both anesthetics are absorbed, could result in higher plasma levels that could, in susceptible individuals, produce a systemic pharmacologic response.

The absorption of EMLA Cream applied to genital mucous membranes was studied in two open-label clinical trials. Twenty-nine patients received 10 g of EMLA Cream applied for 10 to 60 minutes in the vaginal fornices. Plasma concentrations of lidocaine and prilocaine following EMLA Cream application in these studies ranged from 148 to 641 ng/mL for lidocaine and from 40 to 346 ng/mL for prilocaine and time to reach maximum concentration (t_{max}) ranged from 21 to 125 minutes for lidocaine and from 21 to 95 minutes for prilocaine. These levels are well below the concentrations anticipated to give rise to systemic toxicity (approximately 5000 ng/mL for lidocaine and prilocaine).

Distribution: When each drug is administered intravenously, the steady-state volume of distribution is 1.1 to 2.1 L/kg (mean 1.5, ± 0.3 SD, n=13) for lidocaine and is 0.7 to 4.4 L/kg (mean 2.6, ± 1.3 SD, n=13) for prilocaine. The larger distribution volume for prilocaine produces the lower plasma concentrations of prilocaine observed when equal amounts of prilocaine and lidocaine are administered. At concentrations produced by application of EMLA, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 $\mu\text{g/mL}$ of free base) the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins. Both lidocaine and prilocaine cross the placental and blood brain barrier, presumably by passive diffusion.

Metabolism: 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. The metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats (see Carcinogenesis subsection of PRECAUTIONS). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively. Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including *ortho*-toluidine and N-n-propylalanine. It is not metabolized by plasma esterases. The *ortho*-toluidine metabolite has been shown to be carcinogenic in several animal models (see Carcinogenesis subsection of PRECAUTIONS). In addition, *ortho*-toluidine can produce methemoglobinemia following systemic doses of prilocaine approximating 8 mg/kg (see ADVERSE REACTIONS). Very young patients, patients with glucose-6-phosphate deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to methemoglobinemia (see Methemoglobinemia subsection of PRECAUTIONS).

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

Pediatrics: Some pharmacokinetic (PK) data are available in infants (1 month to <2 years old) and children (2 to <12 years old). One PK study was conducted in 9 full-term neonates (mean age: 7 days and mean gestational age: 38.8 weeks). The study results show that neonates had comparable plasma lidocaine and prilocaine concentrations and blood methemoglobin concentrations as those found in previous pediatric PK studies and clinical trials. There was a tendency towards an increase in methemoglobin formation. However, due to assay limitations and very little amount of blood that could be collected from neonates, large variations in the above reported concentrations were found.

Special Populations: No specific PK studies were conducted. The half-life may be increased in cardiac or hepatic dysfunction. Prilocaine's half-life also may be increased in hepatic or renal dysfunction since both of these organs are involved in prilocaine metabolism.

CLINICAL STUDIES

EMLA Cream application in adults prior to IV cannulation or venipuncture was studied in 200 patients in four clinical studies in Europe. Application for at least 1 hour provided significantly more dermal analgesia than placebo cream or ethyl chloride. EMLA Cream was comparable to subcutaneous lidocaine, but was less efficacious than intradermal lidocaine. Most patients found EMLA Cream treatment preferable to lidocaine infiltration or ethyl chloride spray.

EMLA Cream was compared with 0.5% lidocaine infiltration prior to skin graft harvesting in one open label study in 80 adult patients in England. Application of EMLA Cream for 2 to 5 hours provided dermal analgesia comparable to lidocaine infiltration.

EMLA Cream application in children was studied in seven non-US studies (320 patients) and one US study (100 patients). In controlled studies, application of EMLA Cream for at least 1 hour with or without presurgical medication prior to needle insertion provided significantly more pain reduction than placebo. In children under the age of seven years, EMLA Cream was less effective than in older children or adults.

EMLA Cream was compared with placebo in the laser treatment of facial port-wine stains in 72 pediatric patients (ages 5-16). EMLA Cream was effective in providing pain relief during laser treatment.

EMLA Cream alone was compared to EMLA Cream followed by lidocaine infiltration and lidocaine infiltration alone prior to cryotherapy for the removal of male genital warts. The data from 121 patients demonstrated that EMLA Cream was not effective as a sole anesthetic agent in managing the pain from the surgical procedure. The administration of EMLA Cream prior to lidocaine infiltration provided significant relief of discomfort associated with local anesthetic infiltration and thus was effective in the overall reduction of pain from the procedure only when used in conjunction with local anesthetic infiltration of lidocaine.

EMLA Cream was studied in 105 full term neonates (gestational age: 37 weeks) for blood drawing and circumcision procedures. When considering the use of EMLA in neonates, the primary concerns are the systemic absorption of the active ingredients and the subsequent formation of methemoglobin. In clinical studies performed in neonates, the plasma levels of lidocaine, prilocaine, and methemoglobin were not reported in a range expected to cause clinical symptoms.

Local dermal effects associated with EMLA Cream application in these studies on intact skin included paleness, redness and edema and were transient in nature (see ADVERSE REACTIONS).

The application of EMLA Cream to genital mucous membranes for minor, superficial surgical procedures (e.g., removal of condylomata acuminata) was studied in 80 patients in a placebo-controlled clinical trial (60 patients received EMLA and 20 patients received placebo). EMLA Cream (5 to 10 g) applied between 1 and 75 minutes before surgery, with a median time of 15 minutes, provided effective local anesthesia of mucous membranes for minor superficial surgical procedures. The application of EMLA Cream to genital mucous membranes as pretreatment for local anesthetic infiltration was studied in a double blind, placebo-controlled study in 44 female patients (21 patients received EMLA cream and 23 patients received placebo) scheduled for infiltration prior to a surgical procedure of the external vulva or genital mucosa. EMLA Cream applied to the genital mucous membranes for 5 to 10 minutes resulted in adequate topical anesthesia for local anesthetic injection.

Individualization of Dose: The dose of EMLA which provides effective analgesia depends on the duration of the application over the treated area.

All pharmacokinetic and clinical studies on intact skin employed a thick layer of EMLA Cream (1-2 g/10 cm²). The duration of application prior to venipuncture was 1 hour. The duration of application prior to taking split thickness skin grafts was 2 hours. Although a thinner application may be efficacious, such has not been studied and may result in less complete analgesia or a shorter duration of adequate analgesia.

The systemic absorption of lidocaine and prilocaine is a side effect of the desired local effect. The amount of drug absorbed depends on surface area and duration of application. The systemic blood levels depend on the amount absorbed and patient size (weight) and rate of systemic drug elimination. Long duration of application, large treatment area, small patients, or impaired elimination may result in high blood levels. The systemic blood levels are typically a small fraction (1/20 to 1/36) of the blood levels which produce toxicity. Table 2 which follows gives maximum recommended doses, application areas and application times for infants and children.

TABLE 2
EMLA MAXIMUM RECOMMENDED DOSE, APPLICATION
AREA, AND APPLICATION TIME BY AGE AND WEIGHT*
For Infants and Children
Based on Application to Intact Skin

Age and Body Weight Requirements	Maximum Total Dose of EMLA	Maximum Application Area**	Maximum Application Time
0 up to 3 months or <5 kg	1 g	10 cm ²	1 hour
3 up to 12 months and >5kg	2 g	20 cm ²	4 hours
1 to 6 years and >10 kg	10 g	100 cm ²	4 hours
7 to 12 years and >20 kg	20 g	200 cm ²	4 hours

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

* These are broad guidelines for avoiding systemic toxicity in applying EMLA to patients with normal intact skin and with normal renal and hepatic function.

** For more individualized calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults:

The estimated mean(±SD) absorption of lidocaine is 0.045(±0.016) mg/cm²/hr.

The estimated mean(±SD) absorption of prilocaine is 0.077(±0.036) mg/cm²/hr.

An IV antiarrhythmic dose of lidocaine is 1 mg/kg (70 mg/70 kg) and gives a blood level of about 1 µg/mL. Toxicity would be expected at blood levels above 5 µg/mL. Smaller areas of treatment are recommended in a debilitated patient, a small child or a patient with impaired elimination. Decreasing the duration of application is likely to decrease the analgesic effect.

INDICATIONS AND USAGE

EMLA (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on:

- **normal intact skin** for local analgesia.
- **genital mucous membranes** for superficial minor surgery and as pretreatment for infiltration anesthesia.

EMLA is not recommended in any clinical situation in which penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies (see WARNINGS).

CONTRAINDICATIONS

EMLA (lidocaine 2.5% and prilocaine 2.5%) is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS

Application of EMLA to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine and prilocaine resulting in serious adverse effects (see Individualization of Dose).

Studies in laboratory animals (guinea pigs) have shown that EMLA has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to EMLA Cream in the external auditory canal only, showed no abnormality. EMLA should not be used in any clinical situation in which its penetration or migration beyond the tympanic membrane into the middle ear is possible.

Methemoglobinemia: EMLA should not be used in those rare patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents.

Very young patients or patients with glucose-6-phosphate deficiencies are more susceptible to methemoglobinemia.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine, are also at greater risk for developing methemoglobinemia.

There have been reports of significant methemoglobinemia (20-30%) in infants and children following excessive applications of EMLA Cream. These cases involved the use of large doses, larger than recommended areas of application, or infants under the age of 3 months who did not have fully mature enzyme systems. In addition, a few of these cases involved the concomitant administration of methemoglobin-inducing agents. Most patients recovered spontaneously after removal of the cream. Treatment with IV methylene blue may be effective if required.

Physicians are cautioned to make sure that parents or other caregivers understand the need for careful application of EMLA, to ensure that the doses and areas of application recommended in Table 2 are not exceeded (especially in children under the age of 3 months) and to limit the period of application to the minimum required to achieve the desired anesthesia.

Neonates and infants up to 3 months of age should be monitored for Met-Hb levels before, during, and after the application of EMLA, provided the test results can be obtained quickly.

PRECAUTIONS

General: Repeated doses of EMLA 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.

EMLA coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of EMLA in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine, however, EMLA should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Lidocaine and prilocaine have been shown to inhibit viral and bacterial growth. The effect of EMLA on **intra**dermal injections of **live** vaccines has not been determined.

Information for Patients: When EMLA is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Drug Interactions: EMLA should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (see Methemoglobinemia subsection of WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Metabolites of both lidocaine and prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared to the Single Dermal Administration (SDA) of 60 g of EMLA Cream to 400 cm² for 3 hours to a small person (50 kg). The typical application of EMLA Cream for one or two treatments for venipuncture sites (2.5 or 5 g) would be 1/24 or 1/12 of that dose in an adult or about the same mg/kg dose in an infant. The typical application of EMLA Anesthetic Disc for one or two treatments for venipuncture sites (1 or 2 g) would be 1/60 or 1/30 of that dose in an adult or about half the mg/kg dose in an infant.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to 14,400 mg/m²; 60 to 960 times SDA) and rats (900 to 4,800 mg/m²; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple

occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (900 mg/m²; 60 times SDA) was carcinogenic in both species. Thus the no-effect dose must be less than 60 times SDA. The animal studies were conducted at 150 to 2,400 mg/kg in mice and at 150 to 800 mg/kg in rats. The dosages have been converted to mg/m² for the SDA calculations above.

Mutagenesis: The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by the mouse micronucleus test *in vivo*. There was no indication in these three tests of any mutagenic effects.

Ortho-toluidine, a metabolite of prilocaine, (0.5 µg/mL) showed positive results in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with *ortho*-toluidine (300 mg/kg orally; 300 times SDA) were mutagenic for *Salmonella typhimurium* with metabolic activation. Several other tests on *ortho*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation and with single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility: See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies with lidocaine have been performed in rats and have revealed no evidence of harm to the fetus (30 mg/kg subcutaneously; 22 times SDA). Reproduction studies with prilocaine have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus (300 mg/kg intramuscularly; 188 times SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EMLA should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats receiving subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 (w/w). At 40 mg/kg each, a dose equivalent to 29 times SDA lidocaine and 25 times SDA prilocaine, no teratogenic, embryotoxic or fetotoxic effects were observed.

Labor and Delivery: Neither lidocaine nor prilocaine are contraindicated in labor and delivery. Should EMLA be used concomitantly with other products containing lidocaine and/or prilocaine, total doses contributed by all formulations must be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when EMLA is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for prilocaine.

Pediatric Use: Controlled studies of EMLA Cream in children under the age of seven years have shown less overall benefit than in older children or adults. These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

EMLA should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

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

In neonates (minimum gestation age: 37 weeks) and children weighing less than 20 kg, the area and duration of application should be limited (see TABLE 2 in Individualization of Dose).

ADVERSE REACTIONS

Localized Reactions: During or immediately after treatment with EMLA on intact skin, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. Rare cases of hyperpigmentation following the use of EMLA Cream have been reported. The relationship to EMLA Cream or the underlying procedure has not been established. In clinical studies on intact skin involving over 1,300 EMLA Cream-treated subjects, one or more such local reactions were noted in 56% of patients, and were generally mild and transient, resolving spontaneously within 1 or 2 hours. There were no serious reactions which were ascribed to EMLA Cream.

Two recent reports describe blistering on the foreskin in neonates about to undergo circumcision. Both neonates received 1.0 g of EMLA.

In patients treated with EMLA Cream on intact skin, local effects observed in the trials included: paleness (pallor or blanching) 37%, redness (erythema) 30%, alterations in temperature sensations 7%, edema 6%, itching 2% and rash, less than 1%.

In clinical studies on genital mucous membranes involving 378 EMLA Cream-treated patients, one or more application site reactions, usually mild and transient, were noted in 41% of patients. The most common application site reactions were redness (21%), burning sensation (17%) and edema (10%).

Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Systemic (Dose Related) Reactions: Systemic adverse reactions following appropriate use of EMLA are unlikely due to the small dose absorbed (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Systemic adverse effects of lidocaine and/or prilocaine are similar in nature to those observed with other amide local anesthetic agents including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE

Peak blood levels following a 60 g application to 400 cm² of intact skin for 3 hours are 0.05 to 0.16 µg/mL for lidocaine and 0.02 to 0.10 µg/mL for prilocaine. Toxic levels of lidocaine (>5 µg/mL) and/or prilocaine (>6

µg/mL) cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. In the absence of massive topical overdose or oral ingestion, evaluation should include evaluation of other etiologies for the clinical effects or overdosage from other sources of lidocaine, prilocaine or other local anesthetics. Consult the package inserts for parenteral Xylocaine (lidocaine HCl) or Citanest (prilocaine HCl) for further information for the management of overdose.

DOSAGE AND ADMINISTRATION

Adult Patients - Intact Skin

EMLA Cream and Anesthetic Disc

A thick layer of EMLA Cream is applied to intact skin and covered with an occlusive dressing, or alternatively, an EMLA Anesthetic Disc is applied to intact skin:

Minor Dermal Procedures: For minor procedures such as intravenous cannulation and venipuncture, apply 2.5 grams of EMLA Cream (1/2 the 5 g tube) over 20 to 25 cm² of skin surface, or 1 EMLA Anesthetic Disc (1 g over 10 cm²) for at least 1 hour. In controlled clinical trials using EMLA Cream, two sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.

EMLA Cream

A thick layer of EMLA Cream is applied to intact skin and covered with an occlusive dressing:

Major Dermal Procedures: For more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting, apply 2 grams of EMLA Cream per 10 cm² of skin and allow to remain in contact with the skin for at least 2 hours.

Adult Male Genital Skin: As pretreatment prior to local anesthetic infiltration, apply a thick layer of EMLA Cream (1 g/10 cm²) to the skin surface for 15 minutes. Local anesthetic infiltration should be performed immediately after removal of EMLA Cream.

Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. The amount of lidocaine and prilocaine absorbed during the period of application can be estimated from the information in Table 2, ** footnote, in Individualization of Dose.

Adult Female Patients - Genital Mucous Membranes

For minor procedures on the female external genitalia, such as removal of condylomata acuminata, as well as for use as pretreatment for local anesthetic infiltration, apply a thick layer (5 to 10 grams) of EMLA Cream for 5 to 10 minutes.

Occlusion is not necessary for absorption, but may be helpful to keep the cream in place. Patients should be lying down during the EMLA Cream application, especially if no occlusion is used. The

procedure or the local anesthetic infiltration should be performed immediately after removal of EMLA Cream.

Pediatric Patients - Intact Skin

The following are the maximum recommended doses, application areas and application times for EMLA based on a child's age and weight:

Age and Body Weight Requirements	Maximum Total Dose of EMLA	Maximum Application Area	Maximum Application Time
0 up to 3 months or <5 kg	1 g	10 cm ²	1 hour
3 up to 12 months and >5kg	2 g	20 cm ²	4 hours
1 to 6 years and >10 kg	10 g	100 cm ²	4 hours
7 to 12 years and >20 kg	20 g	200 cm ²	4 hours

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

Practitioners should carefully instruct caregivers to avoid application of excessive amounts of EMLA (see Precautions).

When applying EMLA to the skin of young children, care must be taken to maintain careful observation of the child to prevent accidental ingestion of EMLA, the occlusive dressing, or the anesthetic disc. A secondary protective covering to prevent inadvertent disruption of the application site may be useful.

EMLA should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents (see Methemoglobinemia subsection of WARNINGS).

When EMLA (lidocaine 2.5% and prilocaine 2.5%) is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered (see Individualization of Dose). The amount absorbed in the case of EMLA is determined by the area over which it is applied and the duration of application under occlusion (see Table 2, ** footnote, in Individualization of Dose).

Although the incidence of systemic adverse reactions with EMLA is very low, caution should be exercised, particularly when applying it over large areas and leaving it on for longer than 2 hours. The incidence of systemic adverse reactions can be expected to be directly proportional to the area and time of exposure (see Individualization of Dose).

HOW SUPPLIED

EMLA Cream is available in the following:

NDC 0186-1515-01 5 gram tube, box of 1,
contains 2 Tegaderm[®] dressings (6 cm x 7 cm)

NDC 0186-1515-03 5 gram tube, box of 5,

contains 12 Tegaderm[®] dressings (6 cm x 7 cm)

NDC 0186-1516-01 30 gram tube, box of 1

EMLA Anesthetic Disc is available in the following:

NDC 0186-1512-70 1 gram Anesthetic Disc, box of 2

NDC 0186-1512-71 1 gram Anesthetic Disc, box of 10

NOT FOR OPHTHALMIC USE.

KEEP CONTAINER TIGHTLY CLOSED AT ALL TIMES WHEN NOT IN USE.

Store at controlled room temperature 15°-30°C (59°-86°F).

EMLA Anesthetic Disc manufactured by:

Astra Pharmaceutical Production, AB
Södertälje, Sweden

EMLA Cream manufactured by:

▲STRA[®]

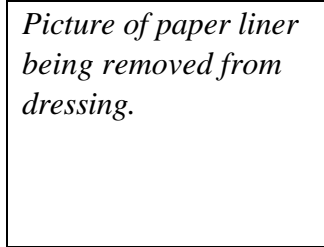
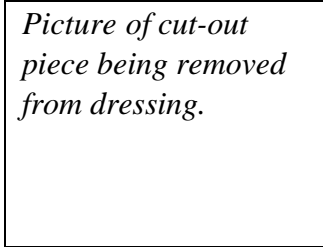
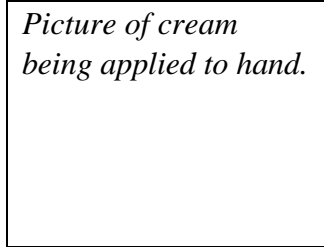
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

NOTE: The following instructions would be on package inserts going into EMLA Cream cartons.

Front of PI

INSTRUCTIONS FOR APPLICATION

EMLA[®] (dollop logo)
Cream (lidocaine 2.5%
and prilocaine 2.5%)

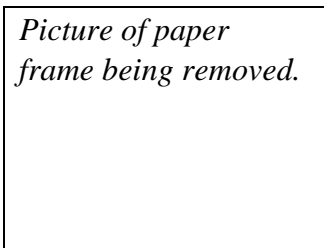
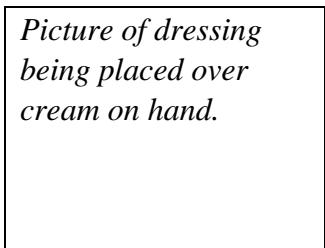


1. In adults, apply 2.5 g of cream (1/2 the 5 g tube) per 20 to 25 cm² (approx. 2 in. by 2 in.) of skin in a thick layer at the site of the procedure.
For pediatric patients, apply ONLY as prescribed by your physician.
If your child is below the age of 3 months or small for their age, please inform your doctor before applying EMLA, which can be harmful, if applied over too much skin at one time in young children.
If your child becomes very dizzy, excessively sleepy, or develops duskiness of the face or lips after applying EMLA, remove the cream and contact your physician at once.

2. Take an occlusive dressing (provided with the 5 g tubes only) and remove the center cut-out piece.

3. Peel the paper liner from the paper framed dressing.
(Instructions continued on reverse side.)

Back of PI



PRECAUTIONS

1. Do not apply near eyes or on open wounds

4. Cover the EMLA[®] Cream so that you get a thick layer underneath. Do not spread out the cream. Smooth down the dressing edges carefully and ensure it is secure to avoid leakage. (This is especially important when the patient is a child.)

5. Remove the paper frame. The time of application can easily be marked directly on the occlusive dressing. EMLA[®] must be applied at least 1 hour before the start of a routine procedure and for 2 hours before the start of a painful procedure.

6. Remove the occlusive dressing, wipe off the EMLA[®] Cream, clean the entire area with an anti-septic solution and prepare the patient for the procedure. The duration of effective skin anesthesia will be at least 1 hour after removal of the occlusive dressing.

2. Keep out of reach of children.


ASTRA[®] 1

Astra USA, Inc.
Westborough, MA
01581

NOTE: The following instructions would be on package inserts going into EMLA AD cartons.

Front of PI

INSTRUCTIONS FOR APPLICATION

EMLA[®] 
Anesthetic Disc
(lidocaine 2.5%
and prilocaine 2.5% cream)
Topical Adhesive System

Picture of EMLA Anesthetic Disc,
with an arrow pointing to the corner.

Picture of the two layers of the
Anesthetic Disc being pulled apart.

1. Make sure that the area to be anesthetized is clean and dry. Take hold of the aluminum flap at the corner of the Anesthetic Disc and bend it backwards. Next, take hold of the corner of the skin-colored Anesthetic Disc layer.

2. Pull the two layers apart, separating the adhesive surface from the protective liner, as shown. Make sure that you do not touch the white, round disc, which contains EMLA.

Back of PI

Picture of Anesthetic Disc being
placed on hand.

Picture of Anesthetic Disc on hand and
time being written with a pen.

PRECAUTIONS

1. Do not apply
near eyes or on
open wounds

2. Keep out of
reach of children.

3. Press firmly around the *edges* of the Anesthetic Disc to ensure good adhesion to the skin. **Do not press on the center of the Anesthetic Disc.** This may cause EMLA to spread under the adhesive.

4. The time of application may be easily marked along the border of the Anesthetic Disc. (A ballpoint pen may be used for this purpose.) EMLA Anesthetic Disc must be applied at least **one hour** before the start of a procedure.

ASTRA[®] 2

Astra USA, Inc.
Westborough, MA
01581