CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-941 / S-012

Trade Name: EMLA Cream

Generic Name: Lidocaine 2.5% and prilocaine 2.5%

Sponsor: AstraZeneca LP

Approval Date: April 20, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-012

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Medical Review(s)	**X**
Chemistry Review(s)	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-012

APPROVAL LETTER

NDA 19-941/S-012
NDA 20-962/S-001

AstraZeneca LP
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

Attention: Lisa DeLuca, Ph.D.
Regulatory Liaison Director

Dear Dr. DeLuca:

Please refer to your supplemental new drug applications dated August 27, 1999, received August 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%), and EMLA® Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5%) Topical Adhesive System.

We acknowledge receipt of your submissions dated October 12, 1999.

These supplemental new drug applications provide for the use of EMLA® Cream and EMLA® Anesthetic Disc Topical Adhesive System for topical dermal analgesia in geriatric patients.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

1. The following statement should be placed in the section entitled CLINICAL PHARMACOLOGY.

   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.

2. The Geriatric Use sub-section should be modified as follows.

   Of the total number of patients in clinical studies of EMLA, 180 were 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDAs 19-941, 20-962
HFD-170/Div. Files
HFD-170/L.Governale
HFD-170/H.Blatt, P.Maturu, C.Schumaker
HFD-170/A.D'Sa, B.Rappaport, R.Uppoor, C.McCormick
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
DISTRICT OFFICE

Drafted by: lg/April 19, 2000
Initialed by: Blatt/4-20-00, Kim/4-20-00, Uppoor/4-20-00, Rappaport/4-20-00
final: Rappaport/4-20-00
filename: 19941.S012(AstraZeneca)AP022300.doc

APPROVAL (AP)

younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of EMLA are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). (See CLINICAL PHARMACOLOGY).

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted August 27, 1999). These revisions are terms of the approval of these applications

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-941/S-012 and 20-962/S-001." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-012

LABELING

721700-09

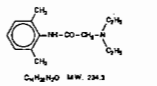
EMLA® CREAM (lidocaine 2.5% and prilocaine 2.5%)

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

DESCRIPTION

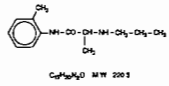
EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than 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:



$C_{14}H_{22}N_2O$ M.W. 234.3

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:



$C_{13}H_{20}N_2O$ M.W. 220.3

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)	C_{max} (µg/mL)	T_{max} (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	583	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 (2.5-15 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 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 µg/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. 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 dehydrogenase 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). 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.

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: 38.6 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 on genital mucous membranes for minor, superficial surgical procedures (eg, 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 for minor superficial surgical procedures. The greatest extent of analgesia, as measured by VAS scores, was attained after 5 to 15 minutes' application. 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 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 > 5 kg	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

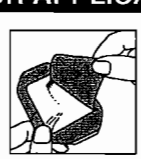
Application of EMLA to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine and prilocaine resulting in serious adverse effects (see Individualization of Dose).

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

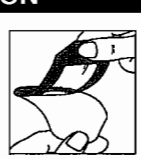
INSTRUCTIONS FOR APPLICATION

EMLA® 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 cm^2 (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.)

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 dehydrogenase 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 paraaminobenzoic 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 intradermal 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 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).

Geriatric Use

Of the total number of patients in clinical studies of EMLA, 180 were age 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of EMLA are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). (See CLINICAL PHARMACOLOGY.)

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 discrete purpuric or petechial reactions at the application site have been reported. 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 (1g 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 an adjunct 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 anesthetic infiltration, apply a thick layer (5-10 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 the 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 cm²	1 hour
3 up to 12 months and > 5 kg	2 g	20 cm²	4 hours
1 to 6 years and > 10 kg	10 g	100 cm²	4 hours
7 to 12 years and > 20 kg	20 g	200 cm²	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 as the following:

NDC 0186-1515-01 contains 2 Tegaderm® dressings (6 cm x 7 cm)	5 gram tube,	box of 1,
NDC 0186-1515-01 Product No. 0186-1515-03 contains 12 Tegaderm® dressings (6 cm x 7 cm)	5 gram tube,	box of 5,
NDC 0186-1516-01 the 30 gram tube of EMLA Cream is packaged in a child resistant tube	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 0186-1512-70 Product No. 0186-1512-71	1 gram Anesthetic Disc,	box of 10

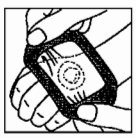
NOT FOR OPHTHALMIC USE.

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

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

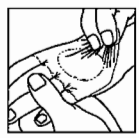
EMLA Anesthetic Disc manufactured for: AstraZeneca LP, Wilmington, DE 19850
by: AstraZeneca AB, Södertälje, Sweden
EMLA Cream manufactured by: AstraZeneca LP, Wilmington, DE 19850
721700-09 Rev. 01/03

AstraZeneca



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 antiseptic 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.

PRECAUTIONS

1. Do not apply near eyes or on open wounds.
2. Keep out of reach of children.

AstraZeneca

AstraZeneca LP, Wilmington, DE 19850
721700-09 Rev. 01/03

721799-05

721799-05

EMLA® CREAM (lidocaine 2.5% and prilocaine 2.5%)

721799-05

EMLA® CREAM (lidocaine 2.5% and prilocaine 2.5%)

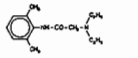
721799-05

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

DESCRIPTION

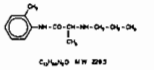
EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than 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:



$C_{14}H_{22}N_2O$ MW 234.3

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:



$C_{13}H_{20}N_2O$ MW 220.3

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 affecting 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 in 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 (cm²)	Time on (hrs)	Drug Content (mg)	Absorbed (mg)	C_{max} (µg/mL)	T_{max} (hr)
60	400	3	lidocaine 1600	54	0.12	4
			prilocaine 1500	82	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 1/30 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 3.0 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 146 to 641 ng/mL for lidocaine and 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 85 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, ±0.2 SD, n=13) for lidocaine and is 0.7 to 4.4 L/kg (mean 2.6, ±1.9 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 µg/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. 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 dehydrogenase 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 85 to 150 minutes (mean 110, ±24 SD, n=13). More than 68% 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.

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 to 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 premyrgical 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 on genital mucous membranes for minor, superficial surgical procedures (eg, 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 10g) applied between 1 and 75 minutes before surgery, with a median time of 15 minutes, provided effective local anesthesia for minor superficial surgical procedures. The greatest extent of analgesia, as measured by VAS scores, was attained after 5 to 15 minutes' application. 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 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 1/30) 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 cm²	1 hour
3 up to 12 months and > 5 kg	2 g	20 cm²	4 hours
1 to 6 years and > 10 kg	10 g	100 cm²	4 hours
7 to 12 years and > 20 kg	20 g	200 cm²	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 this 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 dehydrogenase 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. Those 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 those 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 paraaminobenzoic 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 clinical 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 intradermal 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 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 or 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/fibroadenomas and mesothelioma 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; 100 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 foetotoxic 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).

Geriatric Use

Of the total number of patients in clinical studies of EMLA, 180 were age 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of EMLA are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Localized Reactions: During or immediately after treatment with EMLA on intact skin, the skin of the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. Rare cases of discrete purpuric or petechial reactions at the application site have been reported. 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 50% 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 978 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, tremor, 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 (1g 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 an adjunct 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 anesthetic infiltration, apply a thick layer (5-10 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 the 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 cm²	1 hour
3 up to 12 months and > 5 kg	2 g	20 cm²	4 hours
1 to 6 years and > 10 kg	10 g	100 cm²	4 hours
7 to 12 years and > 20 kg	20 g	200 cm²	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 as the following:

NDC 0186-1515-01	5 gram tube,	box of 1,	contains 2 Tegaderm® dressings (6 cm x 7 cm)
NDC 0186-1515-01 Product No. 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,	the 30 gram tube of EMLA Cream is packaged in a child resistant tube

EMLA Anesthetic Disc is available in the following:

NDC 0186-1512-70	1 gram Anesthetic Disc,	box of 2
NDC 0186-1512-70 Product No. 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 for: AstraZeneca LP, Wilmington, DE 19850
by: AstraZeneca AB, Södertälje, Sweden
EMLA Cream manufactured by: AstraZeneca LP, Wilmington, DE 19850

AstraZeneca

721799-05 Rev. 01/03

INSTRUCTIONS FOR APPLICATION

EMLA®
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.

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 antiseptic 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.

PRECAUTIONS

1. Do not apply near eyes or on open wounds.
2. Keep out of reach of children.

Manufactured by:
AstraZeneca LP, Wilmington, DE 19850

Rev. 01/03

AstraZeneca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-012

MEDICAL REVIEW

NDA 19-941/Geriatric Supplement SLR-012
Sponsor: ASTRA Pharmaceuticals, L.P.
Name: EMLA Cream (lidocaine 2.5% and prilocaine 2.5%)
Type of Submission: Geriatric Labeling Supplement
Proposed Indication: Topical analgesia/anesthesia.
Reviewer: Harold Blatt, D.D.S.
Team Leader: Bob Rappaport, M.D.
Letter Date by Sponsor: August 27, 1999
Date Received by CDER: August 27, 1999
Date Received by Reviewer: December 14, 1999
Date Review Completed: February 1, 2000
CSO: Laura Governale

Background:

This submission is a labeling supplement for "Geriatric Use" of the EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) indicated for topical anesthesia/analgesia indicated for topical anesthesia/analgesia.

Abstract:
The sponsor refers to 21 CFR 201.57(f)(10)(ii)(B) and states that:

- Clinical studies do contain a sufficient number of geriatric patients to determine whether elderly patients respond differently from younger subjects
- Pharmacokinetic documentation does not indicate any dose reduction is necessary in geriatric patients from a safety point of view

Sponsor's Data to Support Geriatric Use Labeling:

The sponsor submitted geriatric additions to the label based on their ISE and ISS, pharmacokinetic studies, post marketing surveillance, and a medical literature review of databases. They found no reports of differences in clinical experience for those subjects compared to younger subjects [Vol. 1.1, p.197.]

ISE:

In the sponsor's ISE, the results of 6 studies were pooled. Of these two were open, randomized, parallel, active controlled studies (86EM20, and 051-27), one was a double blind, randomized, parallel, dose controlled study (85EM14), and 3 were open, single center, uncontrolled studies (800034, 82P033,and 83P030).

On the following page is a summary table (Table 1) of demographic data in all studies included in the sponsor's ISE by age group:

Treat-ment	Age group	Age (years)			Sex		
		Median	Min	max	Male (n)	Female (n)	Total (n)
EMLA	< 65	38.0	14	64	145	76	221
	65-74	70.0	65	74	32	50	82
	>= 75	81.0	75	96	45	55	100
	Missing age	NA	NA	NA	2	0	2
Active control	< 65	32.0	17	64	24	20	44
	65-74	67.0	65	73	4	9	13
	≥ 75	81.0	76	87	3	4	7

[Vol. 1.1, p.120].

The sponsor analyzed the open active controlled trials and found no statistically significant difference in VAS pain scores from the cutting of a split-skin graft between geriatric patients treated with EMLA or Xylocaine infiltration, ($p = 0.256$). [Vol. 1.1, p.124] Analysis of the dose controlled study showed that both geriatric and non-geriatric patient groups felt no or only slight pain during the cutting of the split-skin graft. [Vol. 1.1, p.126]. The statistical analysis performed the three uncontrolled studies showed no statistically significant difference in VRS pain scores from the cutting of a split-skin graft between EMLA-treated geriatric and non-geriatric patients ($p = 0.196$). [Vol. 1.1, p.129.]

Based on the 6 studies in their ISE, the sponsor concluded that efficacy in geriatric patients was not statistically significantly different from the efficacy in non-geriatric patients. [Vol.1.1, p.132.]

ISS:

The ISS summarizes 20 studies on intact skin (including the 6 studies listed in the sponsor's ISE). Studies were divided into three groups. One group included studies on split skin grafting, a second group of intact skin studies in geriatric and non-geriatric patients with electronic data available, and a third group of intact skin studies in just geriatric patients with electronic data available. These studies are listed in the table 2 on the next page:

Category	Blinding	# of studies	Study codes
Split-skin grafting studies			
Active-controlled	Open, randomized	2	86EM20, 051-27
Dose-controlled	Double-blind	1	85EM14
Uncontrolled	Open	3	800034, 82P033, 83P030
Total		6	
Other intact skin studies where data from both geriatric and non-geriatric patients are available in electronic format			
Placebo-controlled single-dose parallel	Double-blind	3	82P003, 6220(051-21), 051-46
Placebo-controlled repeated-dose parallel	Double-blind	1	91EM15
EMLA Cream vs EMLA Anesthetic Disc parallel	Open, randomized	2	051-28, 052-01
EMLA Cream vs EMLA Anesthetic Disc vs placebo crossover	Open, randomized	1	051-36
Uncontrolled repeated-dose	Open	1	051-20
Total		8	
Other intact skin single-dose studies where data from geriatric patients only are available in electronic format			
Placebo-controlled parallel	Double-blind	1	3-EML-03A
Placebo-controlled crossover	Double-blind	1	S80201-405-007*
Active-controlled, crossover	Open, randomized	1	85EM05
Uncontrolled	Open	3	3-EML-01, 84EM01, 87EM11
Total		6	
Grand total		**20**	

Table 2. [Vol. 1.1, p.147.]

From the ISS table above it was found that 5 studies appear to be adequate and well-controlled (randomized, double-blind, and either placebo or dose controlled) for this indication. These studies contained patients over 65 as follows: Study 82P003 had 1 patient, 6220(051-21) had no patients, 051-46 had 12 patients, 3-EML-03A had 1 patient, and S80201-405-007 had 29 patients. (Study 85EM14 was a dose controlled trial and not adequate and well controlled [AWC] and Study 91EM15 was for a different indication.) This totals up to 33 patients over 65. In addition, the sponsor did not provide a breakout of these patients who were 75 or older. However, the total number of patients exposed to EMLA from all the pooled trials is 318. Of this number 138 are 75 or older. These numbers are sufficient to meet the ICH guidelines.

Number of Patients exposed to EMLA in all Studies in the ISS

Age Group	Age (years)			Sex		Total (n)
	Median	Minimum	Maximum	Male (n)	Female (n)	
All split skin grafting studies (Studies 800034, 82P033, 83P030, 85EM14, 86EM20, and 051-27)						
<65	38.0	14	64	145	76	221
65-74	70.0	65	74	32	50	**82**
≥75	81.0	75	96	45	55	**100**
Other controlled and uncontrolled intact skin studies available in electronic format (Studies 82P003, 91EM15, 051-21, 051-28, 051-46, 052-01, 051-20, and 051-36)						
<65	41.0	16.0	64.0	181	118	299
65-74	70.0	65.0	74.0	29	24	**53**
≥75	79.0	75.0	90.0	9	20	**29**
Other intact skin studies (only patients ≥ 65) (Studies 85EM05, S80201, 3EML01, 3EML03A, 84EM01, 87EM11)						
65-74	69.0	65.0	74.0	21	24	**45**
≥75	78.0	76.0	88.0	4	5	**9**

Table 3. [Table based on Tables 2, 6, and 7 Vol. 1.1, pp. 153, 155-156.]

Note: The numbers in bold in the Total (n) column on the right side of the table above represent the source of the number of patients exposed to EMLA that are referred to in the sponsor's labeling. 182 (100+82) geriatric patients were exposed to EMLA in the split skin grafting trials, and 136 (53+29+45+9) geriatric patients were exposed to EMLA in all other trials included in this ISS. The total number of patients exposed comes to 318 (136+182).

Application area (cm^2) in dose controlled and uncontrolled split-skin grafting studies

Uncontrolled	Study Number	n	Median	Q1	Q3	Min	max
< 65 years	800034	92	164	95.0	287.0	24.0	1500.0
	82P033	35	150	77.0	200.0	16.0	348.5
	83P030	16	200	150.0	250.0	75.0	375.0
≥ 65 years	800034	54	130	88.0	200.0	25.0	**500.0***
	82P033	56	130.0	104.5	186.8	42.0	420.0
	83P030	11	150.0	150.0	**180.0***	80.0	200.0

Table 4. [Based on sponsor's table 13, Vol. 1.1, p.161.]
Note: 25% of geriatric patients had an application area of more than 180 cm^2. The maximum application area was 500 cm^2. (See bolded numbers with asterisks). However, this was only for the 121 patients in the dose controlled and uncontrolled split skin grafting studies.

Application time (minutes) in dose-controlled and uncontrolled, split-skin grafting studies

Dose-controlled/ uncontrolled	Study	n	Median	Q1	Q3	Min	Max
< 65 years	800034	92	165	150	220	110	460
	82P033	33	190	155	255	0	350
	83P030	16	150	122.5	150	90	160
	85EM14	45	150	135	210	75	290
	Total	186	165	145	220	0	460
≥65 years	800034	54	177.5	150	215	120	460
	82P033	54	173.5	140	245	77	**495***
	83P030	11	150	135	**165***	120	180
	85EM14	40	165	127.5	192.5	75	300
	Total	159	165	142	215	75	**495***

Table 5. [Based on sponsor's table, Vol. 1.1, p.179.]
Note: 25% of geriatric patients had an application time of at least 165 minutes up to a maximum in excess of 8 hours (up to 495 minutes). See bolded numbers with asterisks in the table above.

Although the sponsor provides information on application area and application time (as shown above) for use in the label, I believe that for the sake of clarity and standardization, language based on that provided in 21 CFR 201.57(f)(10)(ii)(B) would be preferable.

This reviewer looked at the frequency and severity of adverse events in intact skin trials by age group and found the percentages were similar for those over 65 and those 64 and under. Mild application site disorders were 71.9% for those 64 and under and 70.7% for those over 65. They were 4.7% for 64 and under and 3.7% for those over 65 for moderate application site disorders. Skin and appendages were 1.3% for those 64 and under and 1.2% for those over 65. [Vol. 1.1, p.185.]

REVIEW OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Deaths

The only death reported occurred in the placebo-controlled crossover study S80201. A 65 year old woman received about 5 g EMLA to the dorsum of one hand prior to intravenous cannulation for surgery. During the surgery she had a myocardial infarction and died eight hours after EMLA application. The MI was not suspected of having any relationship with the drug. The dose of EMLA was so small and there should be very little percutaneous absorption (systemic plasma levels of lidocaine and prilocaine are not detectable after a dose of 2.5 g EMLA in children.)

Other serious adverse events

There were no other serious adverse events reported in these studies,

Other significant adverse events

Only one significant adverse event was reported in the split-skin grafting study 82P033. A 90-year-old male with prediagnosed arrhythmia suffered a bradycardia. An area of 104 cm^2 on his upper arm had been covered with EMLA for 120 minutes. During the operation his pulse rate was 40-50 beats per minute, which was interpreted as a bradycardia. (Pulse was not checked prior to surgery). He did not experience any discomfort during the operation. The patient had been taking digoxin for ten years for arrhythmia. ECG verified the arrhythmia (atrial fibrillation). The patient left hospital without any sequelae. One month later he was reoperated on with EMLA anesthesia without adverse events. The bradycardia is not suspected of having had any connection with the application of EMLA cream.

Discontinuations due to adverse events

In study S80201 a 68-year-old female patient had extreme shortness of breath before any EMLA had been applied. After application, her anxiety and dyspnea increased, and her procedure was cancelled by the anesthesiologist. The sponsor state that her diagnosis was critical aortic stenosis, with a 70-minute gradient across the aortic valve, an aortic valve area of 0.4 cm^2 and a pulmonary capillar wedge pressure of 28. She was operated on two days later, having exactly the same lab values and symptoms, and this time had no complications during the procedure. The shortness of breath recorded in the CRF was not considered drug related.

In the repeated-dose study 91EM15 an EMLA-treated 20 year old female patient withdrew from the study on day 3 due to mild maceration of the skin at the area of the plastic occlusion. The AE lasted one hour and the patient was completely recovered.

Other safety considerations

EMLA was first introduced in 1984. Most adverse events (AEs) reported were application site reactions. A clinically significant increase in methemoglobin has been observed in a few children; but were thought to be due to concomitant therapy with a

methemoglobin-inducing agent and use in a pre-term infant (where the drug is contraindicated), or due to overdosing.

There has been no case of methemoglobinemia reported in adults.
[Vol. 1.1, pp.170-172.]

Pharmacokinetic Studies:

The sponsor has provided 4 pharmacokinetic studies as follows:
Table 6. [Vol. 1.1, p.27]

Study	Dose / Route of administration	< 65 years	≥65 ≤74 years	≥75 years
Nation (1)	50mg lidocaine IV	7	3	-
Abernethy (2)	25mg lidocaine IV	24	13[1]	
Cusack (3)	250 mg lidocaine PO and 50 mg lidocaine IV	6	6[1]	
Ohlsén (4)	EMLA®Cream 5%	65	20	22

[1] There is no information on the age of the individual subject.

1. *Nation RL, Triggs EJ. Lidocaine kinetics in cardiac patients and aged subjects. British Journal of Clinical Pharmacology 1977; 4: 439-48.* Six elderly (> 60 years of age) long-term stay male residents and four young healthy males were studied. Each subject received 50-mg lidocaine HCl (Xylocaine 0.5% Plain, Astra) injected over 1 min via an antecubital vein. The elimination half-life ($t_{1/2}$) of lidocaine was prolonged in the aged subjects (139.60 $\pm$ 64.09 min) compared with the young individuals (80.58 $\pm$ 9.40 min), whereas the plasma clearance (CL) was similar in both groups

2. *Abernethy DR, Greenblatt DJ. Impairment of lidocaine clearance in elderly male subjects. Journal of Cardiovascular Pharmacology 1983; 5: 1093-6.* Six elderly male (aged 65-75), seven elderly female (aged 64-88), 15 young male (aged 22-38), and nine young female (aged 25-37) volunteers were studied, All subjects received a single intravenous dose of 25mg lidocaine HCl over 30 seconds. $T_{1/2}$ was prolonged in elderly male (2.7 $\pm$ 0.21 h) as compared with young male subjects (1.66 $\pm$ 0.09 h), which was the result of a decrease in CL (12.9 $\pm$ 2.0 versus 19.8+1.5 ml/min/kg). No difference in $t_{1/2}$ was noted among female subjects.

3. *Cusack B, O'Malley K, Lavan J, Noel J, Kelly JG. Protein binding and disposition of lignocaine in the elderly. European Journal of Clinical Pharmacology 1985; 29: 232-9.* This study gave single doses of lidocaine 250 mg orally (lidocaine HC1 capsules, Astra Pharmaceuticals) and 50 mg intravenously over 5 minutes (Xylocaine 2%, Astra Pharmaceuticals) in random order to six young and six elderly nonsmokers. After intravenous administration the plasma-concentration time curves were similar in both groups for the first two hours but then a slower rate of decline occurred in the elderly subjects. However, although the elimination half-life in the geriatric group was 30% longer than in the young volunteers, there was no difference in the volume of distribution

or clearance between the groups. The bioavailability of lidocaine was considerably greater in the older subjects. Binding was higher in the elderly subjects

The findings from three studies on the IV pharmacokinetics of lidocaine in elderly subjects (1, 2, and 3) provide mixed results. In all studies the elimination half-life was statistically significantly longer in elderly than in younger subjects with a 70 % (1), 60 % (2) and 30 % (3) prolongation of the mean elimination half-life, respectively. However, in the second study the half-life was longer only in the male subjects. The longer elimination half-life was due to a larger volume of distribution in the elderly in the first study (1) and to a lower clearance in elderly males in the second study (2), whereas in the third study (3) no significant age-related differences were observed in either volume of distribution or clearance.

4. *Ohlsen L, Englesson S, Evers H. An anesthetic Lidocaine/prilocaine cream (EMLA®) for epicutaneous application tested for cutting split skin grafts. Scand J Plast Reconstr Surg 1985; 19:201-9.* Ohlsen et al. (4) studied the plasma levels of lidocaine and prilocaine following application of EMLA®Cream to the skin for the cutting of split-skin grafts in 107 patients (20 patients between 65-74, 22 patients 75 or older, and 65 patients under 65).

Following application of EMLA® Cream to intact skin areas of up to 375 cm^2 in geriatric patients, mean lidocaine and prilocaine plasma levels were 137 ng/ml and 139 ng/ml, respectively in patients 65-74 years of age (n=20), and 54 ng/ml and 26 ng/ml, respectively in patients >75 (n=22). There was no difference in lidocaine plasma levels on removal or 3 hours after removal of the cream, whereas prilocaine plasma levels were lower on removal of the cream in patients >75 compared to patients <65 years of age (n=65). Consequently, there are no indications on higher systemic plasma levels of lidocaine and prilocaine following application of EMLA® Cream to intact skin in geriatric patients than in non-geriatric patients.

[Vol. 1.1, pp. 27, 29, 31,33.]

Please see PK review for more details regarding these studies.

Post marketing surveillance

The sponsor's review of their post marketing surveillance revealed that, as of 8-6-99, a total of 70 patients 65 or older, 23 of which were 75-90 were included in the safety report database. The sponsor, however, did not provide post marketing data on patients under 65 for comparison. [Vol. 1.1, p.192.]

Other Data:

The sponsor's review of medical literature databases (Medline, Embase, ADIS, LMS Alerts and Delphi Medlit found no reports of differences in clinical experience for those subjects compared to younger subjects [Vol. 1.1, p.197.] This reviewer conducted a

Pubmed search from October of 1999 to December of 1983 that did not reveal sources specific to dosing in the elderly that were not submitted by the sponsor.

Discussion:

Because the overall number of patients exposed to EMLA was 318, the geriatric information available for this product is consistent with 21 CFR 201.57(f)(10)(ii)(B). Namely, that clinical studies do contain a sufficient number of geriatric patients to determine whether elderly patients respond differently from younger subjects but no such differences were observed. This reviewer would prefer that wording be based on that contained in 21 CFR 201.57(f)(10)(ii)(B) are used.

Although approximately 90% lidocaine metabolites and < 10% of lidocaine parent drug administered are excreted through the kidney, systemic exposure of lidocaine prilocaine from EMLA cream is not great. It should also be noted that the metabolite is inactive. Therefore, according to Dr. Shinja Kim , Biopharm Reviewer, and Dr. Ramana Uppoor Biopharm Team Leader, language regarding the standard renal precaution can be omitted. This reviewer concurs with their opinion. For a more detailed discussion of PK issues, see Biopharm review.

Because pharmacokinetic studies were conducted in the elderly, according to 21 CFR 201.57 (f)(10)(iii) (A), they should be described in the "Clinical Pharmacology" section of the labeling as well as the "Geriatric Use" subsection.

WITHHOLD 1 PAGE(S)

Draft labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Anesthetic, Critical Care, and Addiction Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number:	NDA 19-941/S-012 NDA 20-962/S-001
Name of Drug:	EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%), and EMLA® Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5% cream) Topical Adhesive System
Sponsor:	AstraZeneca LP
CSO:	Laura Governale

Material Reviewed

S-012 dated August 27, 1999, compared with latest approved label for S-011 dated January 28, 2000.

Background and Summary Description:

In accordance with 21 CFR 201.57(f)(10), the sponsor submitted a geriatric labeling supplement on August 27, 1999.

Status Report

Reviews Completed: CSO label review – April 20, 2000

CSO Review

Please note that the sponsor's proposed revisions are indicated by strikeovers and underlined text. The agency's proposed revisions will be bolded.

BOX WARNING: N/A

DESCRIPTION: No changes noted.

CLINICAL PHARMACOLOGY: The following statement made by the sponsor should be placed in this section.

> **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.

INDICATIONS AND USAGE: No changes noted.

CONTRAINDICATIONS: No changes noted.

WARNINGS: No changes noted.

PRECAUTIONS: The sponsor proposes to add the following geriatric claim in the last portion of the PRECAUTIONS section.

The Agency prefers to revise the Geriatric Use labeling as follows:

Of the total number of patients in clinical studies of EMLA, 180 were 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of EMLA are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (~2.5 hours) than in younger patients (~1.5 hours). (See CLINICAL PHARMACOLOGY).

The following statement should be placed in the CLINICAL PHARMACOLOGY section as noted previously.

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.

ADVERSE REACTIONS: No changes noted.

DRUG ABUSE AND DEPENDENCE: N/A

OVERDOSAGE: No changes noted.

DOSAGE AND ADMINISTRATION: No changes noted.

HOW SUPPLIED: No changes noted.

This label may be approved with the above revisions.

_____
Consumer Safety Officer

_____
Medical Reviewer Comment/Concurrence

_____
Supervisory Comment/Concurrence

Cc:
Archival NDA 19-941
Archival NDA 20-962
HFD-170/Division Files
HFD-170/L.Governale
HFD-170/C.Schumaker
HFD-170/H.Blatt, B.Rappaport
Initialed by: C.Schumaker/2-10-00, Rappaport/4-20-00
Final: L.Governale/4-20-00, H.Blatt/4-20-00, C.Schumaker/5-1-00

File name: 19941.SLR012(Astra)022500.doc