CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-941 / S-002

Trade Name: **EMLA Cream**

Generic Name: **Lidocaine 2.5% and prilocaine 2.5%**

Sponsor: **AstraZeneca LP**

Approval Date: **April 11, 1994**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-941/S-002

Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

MAR 11 1994

Attention: James G.Baumann,Jr.
Regulatory Affairs

Dear Mr. Baumann:

Please refer to your supplemental new drug application dated December 10, 1993 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA (lidocaine 2.5% and prilocaine 2.5%) Cream.

The supplemental application provides for minor changes to the originally approved package insert.

We have completed our review of this supplemental application with draft labeling and it is approved effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling approved effective as of the date of this letter and the *Instructions for Use* approved December 30, 1992. Marketing the product with FPL that is not identical to this draft labeling and the approved *Instructions for Use* may render the product misbranded and an unapproved drug.

Please submit twelve copies of the FPL as soon as available. Please individually mount seven of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-941/S-002. Approval of this FPL is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available prior to our receipt of the FPL, revision of that labeling may be required.

Should you have any questions, please contact Leslie Vaccari, Project Manager, 301-443-3741.

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

Sincerely yours,

Review Team
Pilot Drug Evaluation Staff, HFD-007
Center for Drug Evaluation and Research

Robert Bedford, M.D.
Medical Officer

Dennis Bashaw, Pharm.D.
Pharmacokineticist

Leslie Vaccari
Project Manager

cc: Orig. NDA19-941/S-002
HFD-007/Div. File
HFD-007/BBedford
HFD-007DBashaw
DO
HFD-85
HFD-007/LVaccari/4-1-94
R/D Init. by: Fran LeSane 4/1/94
F/T by: J.Veach 4/5/94

DOC wp:Emla.02

APPROVED SUPPLEMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-002

LABELING

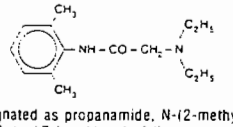
EMLA®
CREAM (lidocaine 2.5% and prilocaine 2.5%)

APPROVED

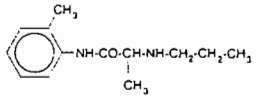
DESCRIPTION

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. A eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals.

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



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



Each gram of EMLA Cream 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 (about 92%) to 1 gram. EMLA Cream 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 Cream (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 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 provided by EMLA Cream depends primarily on the duration of application. To provide sufficient analgesia for clinical procedures such as intravenous catheter placement and venipuncture, EMLA Cream 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 Cream 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.

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

Pharmacokinetics: EMLA Cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% formulated as an oil in water emulsion. As a 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.

The amount of lidocaine and prilocaine systemically absorbed from EMLA Cream 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)	Cmax (μg/mL)	Tmax (hr)
60	400	3	lidocaine 1500	54	0.12	4
			prilocaine 1500	92	0.07	4
60	400	24*	lidocaine 1500	243	0.28	10
			prilocaine 1500	503	0.14	10

*Maximum recommended duration of exposure is 4 hours.

When EMLA Cream is used according to the recommended dosing instructions, 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. The application of EMLA Cream 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. 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 Cream, 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.

It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats (see Carcinogenesis subsection of PRECAUTIONS). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 10% of lidocaine concentrations, respectively. Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including *ortho*-toluidine and N-n-propylalanine. It is not metabolized by plasma esterases. The *ortho*-toluidine metabolite has been shown to be carcinogenic in several animal models (see Carcinogenesis subsection of PRECAUTIONS). In addition, *ortho*-toluidine can produce methemoglobinemia following systemic doses of prilocaine approximating 8 mg/kg (see ADVERSE REACTIONS). Very young patients, patients with glucose-6-phosphate deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to methemoglobinemia (see Methemoglobinemia subsection of PRECAUTIONS).

The half-life of lidocaine elimination from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, ±24 SD, n=13). This half-life may be increased in cardiac or hepatic dysfunction. 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). 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.

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).

Individualization of Dose: The dose of EMLA Cream 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 1/50) of the blood levels which produce toxicity. Table 2 which follows gives maximum recommended application areas for infants and children.

TABLE 2
EMLA CREAM MAXIMUM RECOMMENDED APPLICATION AREA*
For Infants and Children
Based on Application to Intact Skin

Body Weight (kg)	Maximum Application Area (cm²)**
up to 10 kg	100
10 to 20 kg	600
above 20 kg	2000

* 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.

INDICATION AND USAGE

EMLA Cream (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.

EMLA Cream is not recommended for use on mucous membranes because limited studies show much greater absorption of lidocaine and prilocaine than through intact skin. Safe dosing recommendations for use on mucous membranes cannot be made because it has not been studied adequately.

EMLA Cream 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 Cream (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.

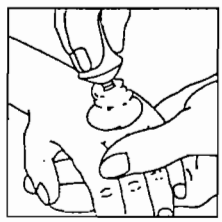
WARNINGS

Application of EMLA Cream 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).

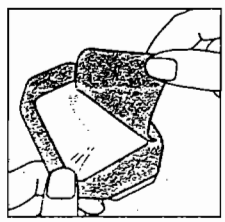
Studies in laboratory animals (guinea pigs) have shown that EMLA Cream has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to EMLA Cream in the external auditory canal only, showed no abnormality. EMLA Cream should not be used in any clinical situation in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

INSTRUCTIONS FOR APPLICATION

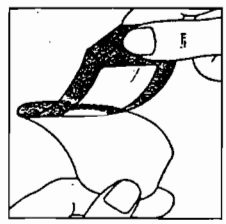
EMLA®
CREAM (lidocaine 2.5% and prilocaine 2.5%)



1. 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.



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.)

Methemoglobinemia: EMLA Cream 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 deficiency 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.

Methemoglobinemia (28%) developed in a three-month old male infant (5.3 kg) who had 5 grams of EMLA Cream under an occlusive dressing applied to the back of the hands and in the cubital regions for 5 hours. The methemoglobinemia was successfully treated with IV methylene blue. The patient was concomitantly receiving trimethoprim (16 mg/day) and sulfamethoxazole (80 mg/day) for a urinary tract infection.

PRECAUTIONS

General: Repeated doses of EMLA Cream may increase blood levels of lidocaine and prilocaine. EMLA Cream 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 Cream 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 Cream in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine; however, EMLA Cream 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.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Metabolites of both lidocaine and prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared to the Single Dermal Administration (SDA) of 60 g of EMLA Cream to 400 cm² for 3 hours to a small person (50 kg). The typical application 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.

A two-year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine, has shown that in both male and female rats 2,6-xylidine in daily doses of 900 mg/m² (60 times SDA) resulted in carcinomas and adenomas of the nasal cavity. With daily doses of 300 mg/m² (20 times SDA), the increase in incidence of nasal carcinomas and/or adenomas in each sex of the rat were not statistically greater than the control group. In the low dose (90 mg/m²; 6 times SDA) and control groups, no nasal tumors were observed. A rhabdomyosarcoma, a rare tumor, was observed in the nasal cavity of both male and female rats at the high dose of 900 mg/m². In addition, the compound caused subcutaneous fibromas and/or fibrosarcomas in both male and female rats and neoplastic nodules of the liver in the female rats with a significantly positive trend test; pairwise comparisons using Fisher's Exact Test showed significance only at the high dose of 900 mg/m². The animal study was conducted at oral doses of 15, 50, and 150 mg/kg/day. The dosages have been converted to mg/m² for the SDA calculations above.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to14,400 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 occurences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/paoillomas 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.

The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results. The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatid exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/mL). No evidence of genotoxicity was found in the *in vivo* assays measuring unscheduled DNA synthesis in rat hepatocytes, chromosome damage in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts from mice. However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions *in vivo*.

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 Cream 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 Cream be used concomitantly with other products containing lidocaine and/or prilocaine, total doses contributed by all formulations should be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when EMLA Cream 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 Cream should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

In children weighing less than 20 kg, the area and duration should be limited (see TABLE 2 in Individualization of Dose).

ADVERSE REACTIONS

Localized Reactions: During or immediately after treatment with EMLA Cream, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. In clinical studies 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.

In patients treated with EMLA Cream, 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%.

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 Cream 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 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

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

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 for at least 1 hour. In controlled clinical trials, two sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.

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.

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.

A single application of EMLA Cream in a child weighing less than 10 kg should not be applied over an area larger than 100 cm². A single application of EMLA Cream in children weighing between 10 kg and 20 kg should not be applied over an area larger than 600 cm² (see Table 2 in Individualization of Dose).

EMLA Cream should not be used in infants under the age of one month or in infants, under the age of twelve months, who are receiving treatment with methemoglobin-inducing agents (see Methemoglobinemia subsection of WARNINGS).

When EMLA Cream (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 Cream 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 Cream 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 0186-1515-03	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	

NOT FOR OPHTHALMIC USE.

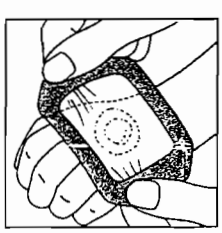
KEEP CONTAINER TIGHTLY CLOSED AT ALL TIMES WHEN NOT IN USE.

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

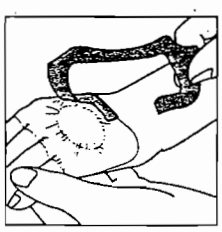
Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
ASTRA® | Astra Pharmaceutical Products, Inc.
Westborough, MA 01581

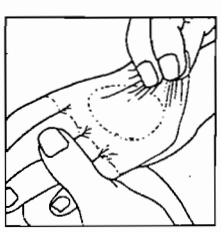
09-091-19-1-80
000425R03 Iss. 12/92



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.

PRECAUTION

1. Do not apply near eyes or on open wounds.
2. Do not use in children under one month of age.
3. Keep out of reach of children.

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000425R03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

APR 1 1994

CSO REVIEW OF LABELING

NDA 19-941/S-002

TRADENAME: EMLA (lidocaine 2.5% and prilocaine 2.5%) Cream

SPONSOR: **Astra USA, Inc.**

SUBMISSION DATE: December 10, 1993
Amendment: March 18, 1994

This labeling supplement provides for minor labeling changes which either clarify or update information already in the insert. Two of the changes provide additions which provide for safer use of the product. The additions are as follows:

1. PRECAUTIONS section

[ ]

2. DOSAGE AND ADMINISTRATION

[ ]

I have checked this draft labeling with the last approved labeling dated December 30, 1992. The only differences noted between the proposed draft labeling and the last approved labeling are those proposed which are acceptable. Therefore, this supplement should be approved.

The medical officer and pharmacokineticist concur that the labeling should be approved.

Leslie Vaccari 4-1-94
Leslie Vaccari
Project Manager

Attachment

cc: ORIG. NDA 19-941/S-002
HFD-007/DIV FILE
HFD-007/CLVaccari/4-1-94
initialed by peer CSO 4/1/94 (date)

DIV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 17, 1993

NDA 19-941

Astra USA, Inc.
P.O. BOX 4500
Westborough, MA 01581-4500

Attention: James G. Baumann, Jr.
Regulatory Affairs Specialist

Dear Mr. Baumann, Jr.,

We acknowledge receipt of your supplemental application for the following:

Name of Drug: EMLA Cream (Lidocaine 2.5% and Prilocaine 2.5%)

NDA Number: 19-941

Supplement Number: S-002

Date of Supplement: December 10, 1993

Date of Receipt: December 16, 1993

Should you have any questions, please contact

Leslie Vaccari
Project Manager
(301) 443- 3741

Sincerely yours,

For Project Manager
Pilot Drug Evaluation Staff,
HFD-007
Center for Drug Evaluation and
Research