

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-941 / S-017

Trade Name: EMLA Cream

Generic Name: Lidocaine 2.5% and prilocaine 2.5%

Sponsor: AstraZeneca LP

Approval Date: December 19, 2005

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APPLICATION NUMBER:

19-941 / S-017

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APPROVAL LETTER



NDA 19-941/S-017

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Judy W. Firor
Director, Regulatory Affairs

Dear Ms. Firor:

Please refer to your supplemental new drug application dated June 16, 2005, received June 17, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA (2.5 % lidocaine and 2.5% prilocaine) Cream.

We acknowledge receipt of your correspondence dated December 12, 2005.

This supplemental new drug application provides for changes to the WARNINGS and PRECAUTIONS sections of the approved package insert based on post-marketing safety surveillance information.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter. As agreed in the correspondence dated December 12, 2005 you will delete the following statement from the PRECAUTIONS: Drug Interactions section of the package insert.

The use of EMLA Cream prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines was not shown to affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared with placebo treated patients.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (text for the package insert). These revisions are terms of the approval of this application.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved supplement NDA 19-941/S-017." Approval of this submission by FDA is not required before the labeling is used.

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If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
12/19/2005 10:35:26 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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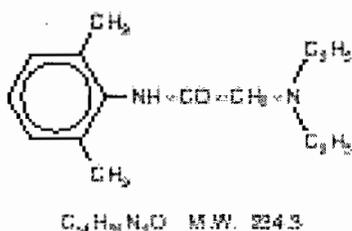
LABELING

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

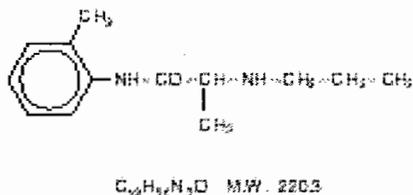
DESCRIPTION

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.

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



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



Each gram of EMLA 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 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 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 Cream depend 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. 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 Cream 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 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. 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 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 Cream (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	503	0.14	10

* Maximum recommended duration of exposure is 4 hours.

When 60 g of EMLA Cream was applied over 400 cm² for 24 hours, peak blood levels of lidocaine are approximately 1/20 the systemic toxic level. Likewise, the maximum prilocaine level is about 1/36 the toxic level. In a pharmacokinetic study, EMLA Cream was applied to penile skin in 20 adult male patients in doses ranging from 0.5 g to 3.3 g for 15 minutes. Plasma concentrations of lidocaine and prilocaine following EMLA Cream application in this study were consistently low (2.5-16 ng/mL for lidocaine and 2.5-7 ng/mL for prilocaine). The application of EMLA 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.

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 Cream, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 $\mu\text{g/mL}$ of free base) the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins. Both lidocaine and prilocaine cross the placental and blood brain barrier, presumably by passive diffusion.

Metabolism: It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity. 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 elimination half-life of lidocaine 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: 38.8 weeks). The study results show that neonates had comparable plasma lidocaine and prilocaine concentrations and blood methemoglobin concentrations as those found in

previous pediatric PK studies and clinical trials. There was a tendency towards an increase in methemoglobin formation. However, due to assay limitations and very little amount of blood that could be collected from neonates, large variations in the above reported concentrations were found.

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

Clinical Studies

EMLA Cream application in adults prior to IV cannulation or venipuncture was studied in 200 patients in

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

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

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

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

EMLA Cream alone was compared with 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 Cream 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 Cream 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 Cream that 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. A thinner application 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 the 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 that produce toxicity. Table 2 below 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 Cream	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 Cream should be restricted to that which corresponds to the patient's weight.

* These are broad guidelines for avoiding systemic toxicity in applying EMLA Cream 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 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.
- **genital mucous membranes** for superficial minor surgery and as pretreatment for infiltration anesthesia.

EMLA Cream is not recommended in any clinical situation when 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).

Patients treated with class III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, dofetilide) should be under close surveillance and ECG monitoring considered, because cardiac effects may be additive.

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 only in the external auditory canal, showed no abnormality. EMLA Cream should not be used in any clinical situation when its penetration or migration beyond the tympanic membrane into the middle ear is possible.

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 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 Cream, 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 Cream, provided the test results can be obtained quickly.

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 should not be applied to open wounds.

Care should be taken not to allow EMLA Cream to come in contact with the eye 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 paraaminobenzoic 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.

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

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.

EMLA Cream should not be applied near the eyes or on open wounds.

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).

Specific interaction studies with lidocaine/prilocaine and class III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, dofetilide) have not been performed, but caution is advised (see WARNINGS).

Should EMLA Cream be used concomitantly with other products containing lidocaine and/or prilocaine, cumulative doses from all formulations must be considered.

~~The use of EMLA Cream prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-Haemophilus influenzae b or Hepatitis B vaccines was not shown to affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared with placebo treated patients.~~

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 with 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.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (450 to 7200 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 (450 mg/m² in mice, 900 mg/m² in rats, 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 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, cumulative doses from all formulations must 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).

When using EMLA Cream 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).

Studies have not demonstrated the efficacy of EMLA Cream for heel lancing in neonates.

Geriatric Use: Of the total number of patients in clinical studies of EMLA Cream, 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 Cream 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 Cream. 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 Cream 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 that 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 Cream.

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 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 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 overdose.

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

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 using EMLA Cream, 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.

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 Cream based on a child's age and weight:

Age and Body Weight Requirements	Maximum Total Dose of EMLA Cream	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 Cream 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 Cream (see PRECAUTIONS).

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

EMLA Cream should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of 12 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 0186-1515-01

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

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 Cream is a trademark of the AstraZeneca group of companies.

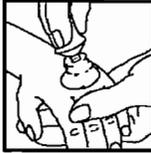
© AstraZeneca 2005

Manufactured by:
AstraZeneca LP, Wilmington, DE 19850

AstraZeneca 

INSTRUCTIONS FOR APPLICATION

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

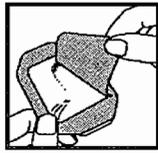


1. In adults, apply 2.5 g of cream (1/2 the 5 g tube) per 20 to 25 cm² (approx. 2 in. by 2 in.) of skin in a thick layer at the site of the procedure.

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 Cream, which can be harmful, if applied over too much skin at one time in young children.

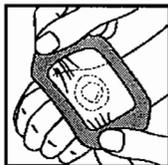
If your child becomes very dizzy, excessively sleepy, or develops duskiess of the face or lips after applying EMLA Cream, remove the cream and contact your physician at once.



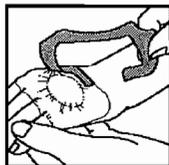
2. Take an occlusive dressing (provided with the 5 g tubes only) and remove the center cut-out piece.



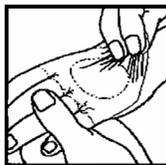
3. Peel the paper liner from the paper framed dressing. (Instructions continued on reverse side.)



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[®] Cream 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



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-017

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

Medical Officer's Review and Evaluation of Clinical Data

NDA # (serial):	19-941 (SLR-017)
Drug Name (generic):	EMLA Cream (lidocaine 2.5% & prilocaine 2.5%)
Sponsor:	AstraZenica LP
Type of Submission:	Labeling Supplement
Date of Submission:	June 16, 2005
Date of Review:	November 30, 2005
Reviewer:	Lex Schultheis, M.D., Ph.D.
Project Manager:	Kim Compton, R.Ph., RPM

1 Background

The Sponsor submitted an amended label containing several significant changes based upon studies reported in the medical literature. A specific warning about the potential for increased toxicity associated with the local anesthetics in EMLA Cream when used with class-III anti-arrhythmic drugs was proposed. A list of class-III drugs was incorporated into the warning. Another change indicates that antibody titers and other measures of successful immunization following vaccination were not significantly different between patients treated with EMLA or placebo prior to injection. Language was inserted to indicate that the efficacy of EMLA for the heel lance procedure in neonates was not established. Other changes included insertion of repeated text advising against application of EMLA on open wounds or the eye and editorial modifications to improve clarity or syntax.

2 Review of Labeling Supplement

- The WARNINGS Section of the Package Insert contains new information regarding the concomitant use of EMLA with class III anti-arrhythmic drugs.

- The PRECAUTIONS Section includes repeated text from the APPLICATION Section advising against use of EMLA on open wounds or in contact with the eye.
- The PRECAUTIONS Section includes repeated text WARNINGS Section of the Package Insert regarding the concomitant use of EMLA with class III anti-arrhythmic drugs.
- The Information for Patients subsection of the PRECAUTIONS Section has had new information added based upon studies reported in the medical literature that EMLA does not affect antibody titers, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titers post immunization as compared with placebo treated patients following certain vaccinations.
- The ADVERSE REACTION Section has been modified to include a statement in the Pediatrics Subsection indicating that the efficacy of EMLA Cream was not established for heel lancing in neonates based upon studies referenced from the medical literature.
- Editorial changes were proposed for incorporation into the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION SECTIONS.

New language proposed by the sponsor is underlined and language proposed for deletion by the sponsor is marked by a single strike though.

PACKAGE INSERT

WARNINGS:

Patients treated with class III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, dofetilide) should be under close surveillance and ECG monitoring considered, because cardiac effects may be additive.

Reviewer's Comments:

The sponsors included a white paper review of local anesthetics and class III anti-arrhythmic as support for their labeling addition. The white paper cites case reports from the medical literature documenting adverse events associated with the use of amiodarone and lidocaine and the Sponsor's own in-house safety data relating symptoms of local anesthetic overdose when class III anti-arrhythmic drugs were used concomitantly with local anesthetics. The sponsor relates decreased clearance of EMLA metabolites to the potential for adverse events associated with concomitant use of lidocaine and class III anti-arrhythmic agents. Blood levels of lidocaine and amiodarone were cited from case reports in the medical literature to support this hypothesis.

Class III anti-arrhythmic (anti-dysrhythmic) drugs can also be proarrhythmic. By prolonging action potential duration (APD) they can lead to a long QT syndrome where early after depolarizations (EADs) can trigger ventricular arrhythmias known as torsades de pointes. Early class III drugs (like sotalol and amiodarone) have properties in addition to increasing APD by blocking K⁺ channels, while the newer class III agents (like sotalol WAY-123,398, dofetilide, E-4031, ibutilide, and RP 58866) are more specific for prolonging refractoriness by selective K⁺ channel blocking activity. Furthermore, even among the new class III agents, differences may exist in their selectivity for the different K⁺ channel types¹.

An ideal class III antiarrhythmic agent, rather than having reverse use dependent APD prolongation, should have little effect during normal sinus heart rates but steeply increase APD as the heart rate accelerates when tachycardia or fibrillation strikes. Further research on these types of drugs may lead to the development of a rate-dependent class III antiarrhythmic agent which could effectively prevent arrhythmias and decrease mortality in treated patients¹.

Class IA agents may also prolong QT interval because they inhibit potassium channel function and the QRS interval by reducing flux through sodium channels. Class IB local anesthetics like lidocaine and prilocaine are sodium channels blockers and prolong the QRS interval, but are unlikely to prolong the QT interval. Class IC drugs block sodium channels in the open position and block potassium channels, like IA agents. IC antiarrhythmics were shown to increase mortality and morbidity compared to placebo in the Cardiac Arrhythmia Suppression Trial of patients having mildly symptomatic ventricular arrhythmias after myocardial infarction^{2,3}.

In summary, the sponsor raises a reasonable concern, regarding concomitant use of EMLA with currently available antiarrhythmic drugs, particularly among agents with class III activity. The statement should be included.

1. New concepts in antiarrhythmic therapy Annual Meeting Refresher course lectures, American Society of Anesthesiology, # 309 pp.1-5. 2005.
2. CAST, New England Journal of Medicine 321: 406-412; 1989
3. Class I and Class III Antiarrhythmic Agents: Mechanisms of Action and the Problem of Proarrhythmic Activity, McGill Journal of Medicine v1 #2 1995

PRECAUTIONS:

General:

EMLA Cream should not be applied to open wounds.

EMLA coming in- Care should be taken not to allow EMLA Cream to come in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation.

NDA 19-941 (S-017)

EMLA[®] Cream (lidocaine 2.5% & prilocaine 2.5%)

Clinical Review of Labeling Supplement

Information for Patients:

EMLA Cream should not be applied to open wounds.

~~EMLA coming in~~ Care should be taken not to allow EMLA Cream to come in contact with the eye ~~should be avoided~~ because animal studies have demonstrated severe eye irritation.

Reviewer's Comment: The sponsor's inclusion reinforces safety information that is likely to be helpful in reducing toxic exposures that have been reported in AERS.

Drug Interactions:

Specific interaction studies with lidocaine/prilocaine and class III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, dofetilide) have not been performed, but caution is advised (see WARNINGS)¹.

Should EMLA Cream be used concomitantly with other products containing lidocaine and/or prilocaine, cumulative doses from all formulations must be considered.

Reviewer's Comment: This information is repeated from the WARNINGS SECTION. It raises a reasonable concern regarding concomitant use of EMLA with currently available antiarrhythmic drugs, particularly among agents with class III activity. The statement is appropriate for the Drug Interactions Subsection.

The use of EMLA Cream prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines was not shown to affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared with placebo treated patients.²

Reviewer's Comment: The Sponsor includes information from the publications listed below to support the proposed statement. The proposal is really a comment on efficacy of other products when used with EMLA and should be supported by source data from adequate and well controlled trials rather than simply summary data from the literature. The findings, if they were adequately supported may be more appropriate for the labels of the vaccines than for EMLA. This information in the EMLA label may also be inappropriately construed as a superiority claim over other products used for prophylactic analgesia in pediatric patients requiring vaccination. In this reviewer's opinion, the statement should not be included in the EMLA label.

1. Wahlgren C-F. Expert Report. Clinical documentation for reclassification of EMLA® cream 5% and EMLA® patch from medical prescription products to non-prescription products. Astra Report No. 802-540-LC-0137, June 16, 1999.

2. Halperin SA. A randomized, double-blind, placebo-controlled trial to measure the antibody response to immunization with measles-mumps-rubella vaccines using EMLA® patch for the reduction of pain associated with subcutaneous injection in twelve month old infants. Astra Report No. 802-540-LC-0122-01, December 18, 1998.
3. Halperin SA. A randomized, double-blind, placebo-controlled trial to evaluate the antibody response to immunisation with diphtheria-tetanus-pertussis-inactivated poliovirus-*Haemophilus influenzae b* and hepatitis B vaccines using EMLA® patch for the reduction of pain associated with intramuscular injection in infants from birth to six months of age. Astra Report No. 802-540-LC-0145-01, November 11, 1999.
4. Dohlwitz A, Hellenberg L, Svedmyr J, Tober L, Wigertz A. No negative influence of EMLA application prior to BCG vaccination. Acta Paediatr 1998;87(4):480-81.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to 14,400 450 to 7200 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 (450 mg/m² in mice, 900 mg/m² in rats, 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.

Reviewer's Comment:

In the sponsor's revision, doses and safety margins have been re-calculated. The factors for converting a mg/kg (body weight) dose to mg/m² (surface area) are 3 for mice and 6 for rats. The sponsor comments that in the previous calculations a factor of 6 had been used erroneously for both mice and rats. These corrections may be included.

Pediatric Use:

Studies have not demonstrated the efficacy of EMLA Cream for heel lancing in neonates^{3,4,5}.

Reviewer's Comment: The sponsor included publications (referenced below) from the medical literature to support this statement. Although the data is of a summary nature, this statement is likely to benefit patients because there is no evidence to support the use of EMLA in this setting and there is risk associated with its use. The statement should be included.

1. Stevens b, Johnston C, Taddio A, Koren G Aranda J, The safety and efficacy of EMLA for heel lancing in preterm neonates World Congress on Pain; 1996:181-182. Abstract 239
2. Larsson BA, Jylli L, Lagercrantz H, Olsson GL, Does a local anaesthetic cream (EMLA) alleviate pain from heel-lancing in neonates? Acta Anaesthesiol Scand 1995: 23:: 1028-1031

3 Reviewer's Summary Comments:

The sponsor's proposed additions to WARNINGS SECTION and the PRECAUTIONS SECTION about the use of EMLA with antiarrhythmic drugs may improve safe use of EMLA and may be accepted. The proposed addition to the PRECAUTIONS SECTION indicating that EMLA should not be applied to open wounds addresses a known safety concern and is acceptable. The proposed addition to the Drug Interaction subsection of PRECAUTIONS regarding concomitant use of EMLA with antiarrhythmic drugs supports the addition in labeling and is acceptable. In contrast, the Sponsor's proposal regarding concomitant use of EMLA with pediatric vaccines to the Drug Interaction subsection of PRECAUTIONS is promotional and should not be accepted. The Sponsor's recalculation of toxic dosing in the Carcinogenesis subsection of Carcinogenesis, Mutagenesis, Impairment of Fertility is more conservative than the current label and is acceptable. The proposed addition to the Pediatric Use subsection of PRECAUTIONS is acceptable because the statement will reduce risk in a setting where there is evidence of no clinical benefit.

4 Recommendations: Approval of S-017 is recommended with the modifications suggested above.

Lex Schultheis, M.D., Ph.D.	Date
Medical Officer	11/7/05

Comments that may be shared with the Sponsor:

Your proposed labeling change to the Drug Interaction subsection of PRECAUTIONS regarding concomitant use of EMLA Cream with pediatric vaccination is a comment on efficacy markers of vaccination products when used with EMLA. Data from adequate and well controlled trials will be needed to be submitted for review before this labeling change can be considered.

The remaining changes proposed to the EMLA label in SLR-017 are acceptable.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lester Schultheis
12/5/2005 02:37:29 PM
MEDICAL OFFICER

Arthur Simone
12/5/2005 02:44:12 PM
MEDICAL OFFICER
I have read Dr. Schultheis' review and concur with
his comments and recommendations.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-017

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Division of Anesthesia, Analgesia and Rheumatology Products

REGULATORY PROJECT MANAGER LABEL REVIEW

Application Number: N 19-941/S-017

Name of Drug: Emla cream (lidocaine 2.5% and prilocaine 2.5%)

Sponsor: AstraZeneca LP

Material Reviewed

Submission Date(s): June 16, 2005

Receipt Date(s): June 17, 2005

Background and Summary Description:

In addition to removing references to the EMLA Anesthetic Disc product (N 20-962), which has been withdrawn from the market for business reasons, the sponsor proposes changes to the DESCRIPTION, WARNINGS, and PRECAUTIONS sections of the label. The proposed labeling for this supplement was compared to the final printed labeling for S-015 (supplement approved 1-27-03), submitted 6-23-03, and acknowledged and retained on 12-20-03.

Reviews Completed: Amarantha Birkel, 6-30-05; Lex Schultheis, M.D., Medical Officer, 12-5-05; Dan Mellon, Ph.D., Supervisory Pharmacologist, 12-13-05.

Review

Please note that the sponsor's proposed omissions are indicated by strikeouts, inclusions by underlined text.

Overview-

Throughout the Package Insert (PI) the sponsor had removed references to their similar formulation lidocaine and prilocaine product, EMLA Anesthetic Disc (N 20-962), which has been withdrawn from the market for business reasons.

HEADER:

The portion of the header referring to the Disc has been removed

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

BOX WARNING: N/A

DESCRIPTION:

The following material referring to the Disc has been removed from this section:

~~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 10cm². The surface area of the entire anesthetic disc is approximately 40cm².~~

CLINICAL PHARMACOLOGY:

In the "Mechanism of Action" subsection, an editorial change has been made to the 1st sentence of the 2nd paragraph as follows:

The onset, depth and duration of dermal analgesia on intact skin provided by EMLA cream depends primarily on the duration on application.

In the "Elimination" section of the Pharmacokinetics subsection, the following editorial change has been made:

The elimination half-life of lidocaine ~~elimination~~ from the plasma following IV administration is approximately etc.

CLINICAL STUDIES:

In the 5th paragraph of this section the following editorial change has been made:

EMLA Cream alone was compared to with EMLA Cream followed by lidocaine infiltration and lidocaine infiltration alone prior etc.

The following changes have been made to the 1st paragraph of the "Individualization of Dose" subsection:

The dose of EMLA Cream ~~which~~ that provides effective analgesia depends on the duration of the application over the treated area. All Pharmacokinetic...2 hours. ~~Although a~~ 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 following editorial changes have been made to the 2nd paragraph of the "Individualization of Dose" subsection:

The systematic blood levels depend on the amount absorbed and patient size (weight) and the rate of systemic drug elimination. Long duration...blood levels. The systematic blood levels are typically a small fraction (1/20 to 1/36) of the blood levels ~~which~~ that produce toxicity. Table 2 ~~which follows~~ below gives maximum recommended doses...

INDICATIONS AND USAGE:

The following editorial change has been made to the last paragraph of this section:

EMLA Cream is not recommended in any clinical situation ~~in which~~ when 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: No changes were made.

WARNINGS:

The following material was added as a 2nd paragraph in this section:

Patients treated with class III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, defetilide) should be under close surveillance and ECG monitoring considered, because cardiac effects may be additive.

The following editorial changes have been made to the 3rd paragraph of this section:

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

PRECAUTIONS:

The following sentence has been added as a 2nd paragraph to this section:

EMLA cream should not be applied to open wounds.

The 1st sentence of the 3rd paragraph has been altered as follows:

~~EMLA coming in~~ Care should be taken not to allow EMLA Cream to come in contact with the eye ~~should be avoided~~ because animal studies have demonstrated severe eye irritation.

The following sentence has been added in the “Information for Patients” subsection:

EMLA Cream should not be applied near the eyes or on open wounds.

The following material has been added to become the 3-5th paragraphs of the “Drug Interactions” subsection:

Specific interaction studies with lidocaine/prilocaine and class III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, dofetilide) have not been performed, but caution is advised (see WARNINGS).

Should EMLA cream be used concomitantly with other products containing lidocaine and/or prilocaine, cumulative doses from all formulations must be considered.

The use of EMLA Cream prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus- *Haemophilus influenzae b* or Hepatitis B vaccines was not shown to affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared with placebo treated patients.

The following editorial change has been made in the “Carcinogenesis, Mutagenesis, Impairment of Fertility” subsection:

In the animal studies reported below, doses or blood levels are compared ~~to~~ with 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...~~infant.~~ Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (~~900 to 14,400~~ 450 to 7200 mg/m²; 60 to 960 times SDA) and rats (900 to 4800 mg/m²; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors...~~female rats.~~ The lowest dose tested (450 mg/m² in mice, 900 mg/m² in rats, 60 times SDA) was carcinogenic in both species.

The following change to the 2nd sentence of the “Labor and Delivery” subsection was made:

Should EMLA cream be used concomitantly with other products containing lidocaine and/or prilocaine, ~~total cumulative doses contributed by~~ from all formulations must be considered.

The following sentence has been added as the last paragraph of the “Pediatric Use” subsection:

Studies have not demonstrated the efficacy of EMLA cream for heel lancing in neonates.

ADVERSE REACTIONS:

The following editorial change to the last sentence of the “Localized Reactions” subsection was proposed:

There were no serious reactions ~~which~~ that were ascribed to EMLA cream.

DRUG ABUSE AND DEPENDENCE: N/A

OVERDOSAGE: No Changes were made.

DOSAGE AND ADMINISTRATION:

Reference to the Disc in the “Minor Dermal Procedures” subsection was removed as follows:

For minor procedures such as intravenous cannulation and venipuncture, apply 2.5 grams of EMLA cream (1/2 the 5g tube) over 20 to 25cm² of skin surface, ~~or 1 EMLA Anesthetic Disc (1g over 10cm²)~~ for at least 1 hour. In controlled...

Immediately following this subsection, the subsection entitled "EMLA Cream" was deleted:

~~EMLA Cream~~

~~A thick layer of EMLA Cream is applied to intact skin and covered with an occlusive Dressing.~~

The following editorial change was made to the 5th paragraph of the "Pediatric Patients-Intact Skin" subsection:

EMLA Cream should not be used in neonates with a gestational age less than 37 weeks nor infants under the age on ~~twelve~~ 12 months who are receiving treatment with methemoglobin-inducing agents (see Methemoglobin subsection of WARNINGS).

HANDLING AND DISPOSAL: N/A

HOW SUPPLIED:

Reference to the Disc was removed from the label:

~~EMLA Anesthetic Disc is available in the following:~~

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

~~NDC 0186 1512 70~~

~~Product No. 0186 1512 71 — 1 gram Anesthetic Disc, — box of 10~~

The year of the copyright was updated as follows:

©AstraZeneca ~~2004~~, 2005

The label version and revision number were updated as follows:

~~721700-09~~ Rev. ~~01/03~~

Recommendation:

The Pre-Clinical team has reviewed the proposed changes to the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label and feels that the changes proposed for that section of the label are acceptable.

The clinical team agreed with the proposed changes, except the addition of the proposed change to the "Drug Interactions" subsection of PRECAUTIONS regarding concomitant use of EMLA Cream with pediatric vaccination is a comment on efficacy markers of

vaccination products when used with EMLA. Data from adequate and well controlled trials will need to be submitted for review before this labeling change can be considered.

Therefore, the sponsor was contacted on 12-8-05, and asked if they would agree to remove this proposed change. The sponsor subsequently agreed to remove this language in an amendment to the sNDA dated 12-12-05 and so the sNDA, as amended, should be approved.

Initial review completed by Amarantha Birkel/6-30-05

Finalized by Kim Compton, 12-15-05.

Concurred by Sara Stradley, 12-15-05

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/s/

Kimberly Compton
12/15/2005 05:10:26 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19850-8355

Attention: Judy W. Firor
Director, Regulatory Affairs

Dear Ms. Firor:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: EMLA (2.5 % lidocaine and 2.5% prilocaine) Cream.
NDA Number: 19-941
Supplement number: S-017
Date of supplement: June 16, 2005
Date of receipt: June 17, 2005

This supplemental application proposes changes to the WARNINGS and PRECAUTIONS sections of the approved package insert based on post-marketing safety surveillance information.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 16, 2005, in accordance with 21 CFR 314.101(a).

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

Food and Drug Administration

NDA 19-941/S-017

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Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170
Attention: Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions call me at (301) 827-7432.

Sincerely yours,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kimberly Compton
6/29/05 11:17:22 AM