19-941/S-011

NDA 19-941/S-011

AstraZeneca LP
725 Chesterbrook Boulevard
Wayne, Pennsylvania 19087-5677

Attention: Brian A Green
RA Specialist

Dear Mr. Green:

Please refer to your supplemental new drug application (sNDA) dated March 29, 1999, received March 31, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA® Cream (2.5% lidocaine, 2.5% prilocaine).

We also refer to your amendments dated May 20, 25, October 18, November 1, 8, December 17, 21, 1999, and January 18, 2000.

This supplemental new drug application provides for the use of EMLA Cream as topical anesthetic for superficial minor surgery of genital mucuos membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA 19-941/S-011." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until January 28, 2001. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

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

Please submit one market package of the drug product when it is available.

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

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

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

Enclosure: Approved Draft Package Insert

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

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

DESCRIPTION

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals. It is packaged in 5 gram and 30 gram tubes. It is also packaged in the Anesthetic Disc, which is a single-dose unit of EMLA contained within an occlusive dressing. The Anesthetic Disc is composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring. The disc contains 1 gram of EMLA emulsion, the active contact surface being approximately 10 cm^2. The surface area of the entire anesthetic disc is approximately 40 cm^2.

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:

molecular structure

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

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:

molecular structure

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

Absorption: The amount of lidocaine and prilocaine systemically absorbed from EMLA is directly related to both the duration of application and to the area over which it is applied. In two pharmacokinetic studies, 60 g of EMLA Cream (1.5 g lidocaine and 1.5 g prilocaine) was applied to 400 cm^2 of intact skin on the lateral thigh and then covered by an occlusive dressing. The subjects were then randomized such that one-half of the subjects had the occlusive dressing and residual cream removed after 3 hours, while the remainder left the dressing in place for 24 hours. The results from these studies are summarized below.

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

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

* Maximum recommended duration of exposure is 4 hours.

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

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

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

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

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

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

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

CLINICAL STUDIES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The estimated mean(±SD) absorption of lidocaine is 0.045(±0.016) mg/cm^2/hr.

The estimated mean(±SD) absorption of prilocaine is 0.077(±0.036) mg/cm^2/hr.

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

PRECAUTIONS

General: Repeated doses of EMLA may increase blood levels of lidocaine and prilocaine. EMLA should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and prilocaine including acutely ill, debilitated, or elderly patients.

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

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Metabolites of 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 cm^2 for 3 hours to a small person (50 kg). The typical application of EMLA Cream for one or two treatments for venipuncture sites (2.5 or 5 g) would be 1/24 or 1/12 of that dose in an adult or about the same mg/kg dose in an infant. The typical application of EMLA Anesthetic Disc for one or two treatments for venipuncture sites (1 or 2 g) would be 1/60 or 1/30 of that dose in an adult or about half the mg/kg dose in an infant.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to 14,400 mg/m^2; 60 to 960 times SDA) and rats (900 to 4,800 mg/m^2; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple

occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (900 mg/m^2; 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/m^2 for the SDA calculations above.

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

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

Impairment of Fertility: See Use in Pregnancy.

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

OVERDOSAGE

Peak blood levels following a 60 g application to 400 cm^2 of intact skin for 3 hours are 0.05 to 0.16 μg/mL for lidocaine and 0.02 to 0.10 μg/mL for prilocaine. Toxic levels of lidocaine (>5 μg/mL) and/or prilocaine (>6

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

DOSAGE AND ADMINISTRATION

Adult Patients - Intact Skin

EMLA Cream and Anesthetic Disc

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

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

EMLA Cream

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

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

Adult Male Genital Skin: As pretreatment prior to local anesthetic infiltration, apply a thick layer of EMLA Cream (1 g/10 cm^2) to the skin surface for 15 minutes. Local anesthetic infiltration should be performed immediately after removal of EMLA Cream.

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

Adult Female Patients - Genital Mucous Membranes

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

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

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

Pediatric Patients - Intact Skin

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

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

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

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

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

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

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

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

HOW SUPPLIED

EMLA Cream is available in the following:

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

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

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

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

EMLA Anesthetic Disc is available in the following:

NDC 0186-1512-70	1 gram Anesthetic Disc,	box of 2
NDC 0186-1512-71	1 gram Anesthetic Disc,	box of 10

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

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

EMLA Anesthetic Disc manufactured by:

Astra Pharmaceutical Production, AB
Södertälje, Sweden

EMLA Cream manufactured by:

ASTRA

Astra Pharmaceuticals, L.P.
Wayne, PA 19087

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

Front of PI

INSTRUCTIONS FOR APPLICATION

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

Picture of cream being applied to hand.	*Picture of cut-out piece being removed from dressing.*	*Picture of paper liner being removed from dressing.*

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

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

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

Back of PI

Picture of dressing being placed over cream on hand.	*Picture of paper frame being removed.*	*Picture of dressing being removed from hand.*

PRECAUTIONS

1. Do not apply near eyes or on open wounds

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

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

6. Remove the occlusive dressing, wipe off the EMLA® Cream, clean the entire area with an 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.

2. Keep out of reach of children.

ASTRA 1

Astra USA, Inc.
Westborough, MA
01581

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

Front of PI

INSTRUCTIONS FOR APPLICATION

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

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

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

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

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

Back of PI

Picture of Anesthetic Disc being placed on hand.

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

PRECAUTIONS

1. Do not apply near eyes or on open wounds

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

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

2. Keep out of reach of children.

ASTRA 2

Astra USA, Inc.
Westborough, MA
01581

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

Brand Name: EMLA® Cream

Generic Name: lidocaine 2.5% and prilocaine 2.5%

Indication: Topical anesthesia for superficial minor surgery of genital mucous membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes.

NDA Classification: SE 1-011

NDA Number: 19-941

Original Receipt Date: March 31, 1999

Clinical Reviewer: Harold J. Blatt, D.D.S.

Review Completed: January 7, 2000

TABLE OF CONTENTS

SECTION 1.0 MATERIALS UTILIZED IN REVIEW

Reviewer's Table 1. Materials utilized in Review

Volume	Submission Date	Material
44.1	3-31-99	Overview, proposed labeling
44.1-44.7	3-31-99	Summary of Clinical Trials and Clinical Study Reports
44.8	3-31-99	Literature References
44.9	3-31-99	Astra Summary Documents

SECTION 2.0 BACKGROUND

SECTION 2.1 INDICATION:

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

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

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

[From sponsor's proposed label, Vol. 44.1, pp.16-17]

SECTION 2.2 RELATED INDs AND NDAs:

SECTION 2.3 ADMINISTRATIVE HISTORY

NDA 19-941 EMLA ® Cream, was approved December 30, 1992, as a topical anesthetic for use on normal intact skin for local analgesia. On February 4, 1998, EMLA (NDA 19-941/S-008) was approved as safe and effective as an adjunct to local infiltration anesthesia on male genital skin after a minimum application time, under occlusion, of 15 minutes.

The sponsor has submitted this current supplement to provide both old and new documentation to support the safe and effective use of EMLA as a topical anesthetic for superficial minor surgery of genital mucous membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes.

The sponsor feels that available topical anesthetic formulations, such as 20% benzocaine gel or spray, have been tested in double-blind trials for some of the moderately painful gynecologic procedures without convincing evidence of efficacy. Therefore the sponsor feels, there is a need for an effective topical anesthetic that can be painlessly applied to the genital mucous membranes prior to minor surgical procedures and local anesthetic injections..

This current submission contains 14 non-US trials (four pivotal, six supportive, and four involving either a different concentration of EMLA (2%) or different indication, four human PK studies, and four non-clinical Pharm/Tox studies.

[Vol. 44.1, pp.1, 2]

SECTION 2.4 PROPOSED DIRECTIONS FOR USE:

"DOSAGE AND ADMINISTRATION

"Adult Patients - Intact Skin

"EMLA Cream and Anesthetic Disc

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

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

"EMLA Cream

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

"Major Dermal Procedures: For more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting, apply 2 grams of EMLA Cream per 10 cm 2 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 cm 2) 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 Patients - Genital Mucous Membranes

"For minor procedures involving the cervix, such as cervical curettage and cervical biopsy,

apply 5 grams of FMLA Cream in each of the lateral vaginal fornices for 10 minutes. For minor surgical procedures on the external genitals, such as removal of condylomata acuminata and vulval biopsies, as well as for use as an adjunct prior to local anesthetic infiltration, apply a thick layer (5 to 10 grains) of EMLA Cream for 5 to 10 minutes.

"Occlusion is not necessary for absorption, but may be helpful to keep the cream in place. Female patients should be lying down during the EMLA Cream application, especially if no occlusion is used. The procedure or the local anesthetic infiltration should be performed immediately after removal of EMLA Cream.

"Pediatric Patients - Intact Skin

"The following are the maximum recommended doses, application areas and application times for EMLA based on a child's age and weight:
Reviewer's Table 2.

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

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

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

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

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

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

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

[Taken from sponsor's proposed label, Vol. 44.1, pp. 21-22.]

SECTION 2.5 FOREIGN MARKETING

EMLA is currently approved for use on mucous membranes in the following 36 countries:

Argentina, Austria, Belgium, 13razil, Canada, Czech Republic, Cyprus, Denmark, Finland, France, Greece, Indonesia, Ireland, Italy, Lithuania, Luxembourg, Netherlands, Norway, Paraguay, Peru, Poland, Portugal, Rumania, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, UK,

United Arab Emirates, Uruguay, Yugoslavia.

SECTION 3.0 CHEMISTRY

N/A

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The sponsor has summarized the pharm/tox data for EMLA in Vol. 44.1, pp.42-45 of the Supplement. The following is a condensation of that summary:

Two nonclinical studies designed to evaluate the local tolerance of the vaginal and uterine mucous membranes when treated with EMLA Cream were conducted in dogs. A third study in dogs was performed to investigate the general toxicity after repeated doses of EMLA Cream administered rectally. The observations in all three studies showed little or no effects following the application of EMLA, and the cream was well tolerated by the. genital mucous membranes. Rectal administration was chosen for the repeat dose study as this route provided a practically acceptable way of obtaining sufficiently high systemic exposure to the test compounds.

A pharmacokinetic evaluation was included in two of the studies (one of which was reported in a separate report). The plasma levels of both lidocaine and prilocaine remained substantially below known human toxic levels for these compounds (5-6μg/mL). These three studies are summarized below, as well as the one pharmacokinetic study report.

Study 83019 (Report 802-10 T1517)
Local Toxicity of EMLA in Female Dogs After Single Administration into the Uterine Cavity via Laparotomy

The purpose of this study was to determine the local toxicity of EMLA in the uterine and oviductal tissues after a single administration into the uterine cavity of dogs. All animals

recovered well from the surgery. and no clinical signs of toxicity developed during the 3-day observation period. The uterus appeared to be morphologically normal in all dogs. All dogs showed good appetite during the study. All dogs showed a slight reduction in body weight directly after surgery due to the pre-- and postoperative fasting periods. However, all dogs had increased in weight by the day of sacrifice. All rectal temperature values were within normal limits. No changes that could be related to the treatment with the test article were detected.

Study 80001 (Report 802-10 T1163)
Vaginal Irritation, in Dogs, After Topical Administration of Xylocaine ®/Citanest® (EMLA) on 20 Consecutive Days

The purpose of this study was to investigate the local tolerance of EMLA Cream after daily vaginal administration in beagles for 20 days. Pharmacokinetic data were also collected. The body weight, rectal temperature and food consumption of all animals was normal throughout the trial. Examination of the vaginal mucosa 1 hour after treatment revealed a slight increase in erythema in both groups, with a tendency towards a somewhat more persistent reaction in the EMLA treated group. At 24 hours after treatment, the reaction in the placebo group had, for the most part, regressed to the level noted before treatment. In the EMLA treated animals, the reaction after 24 hours was similar to that noted after one hour. However, even before treatment commenced, 4 of the 12 dogs had increased erythema on one or more of the examination occasions. An investigation of the vaginal microbiological flora did not indicate any changes that might be a result of application of the formulations. Pathological examination of the genital organs did not reveal any adverse effects of treatment.

Maximum plasma concentrations of both lidocaine (320-565 ng/mL) and prilocaine (155-260 ng/mL) were reached about 10-45 minutes after single vaginal administration of EMLA. The levels of prilocaine were consistently one-half those of lidocaine. The systemic availability after single vaginal administration was calculated to be 33-77% for lidocaine and 40-86% for prilocaine. This suggests by-pass of the liver, thus reducing hepatic first pass elimination of the test compounds. The systemic availability of both lidocaine and prilocaine increased by about 40% following repeated administration.

Study 83040 (Report 802-10 T1608)
General Toxicity of EMLA Given Rectally to Dogs for One Month

The purpose of this study was to determine the general toxicity of EMLA Cream after daily rectal administration to dogs for one month. No clinical signs of dysfunction or local irritation were noted. There were no significant changes in body weight or food consumption during the study. All rectal temperature values were within normal limits. There were no ECG changes or signs of ophthalmic disorders related to treatment during the study. Also, no changes in hematology, blood chemistry or urinalysis related to treatment were noted. Finally, there were no changes in the histopathology that could be related to treatment.

Report#802-10AF42-1
Evaluation of Plasma Concentrations of Lidocaine and Prilocaine in the Study:
General and Local Toxicity of EMLA Given Rectally to Dogs for One Month

The purpose of this study was to determine the pharmacokinetics of lidocaine and prilocaine after rectal administration of EMLA Cream in beagle dogs for 21-23 days. This analysis was part of Study 83040 (Report 802-10 T1608).

Daily rectal administration of EMLA Cream to dogs for 21-23 days resulted in a fairly rapid absorption of both lidocaine and prilocaine into the general circulation (t_{max} 0.5 to 1.0 hours). There was no significant difference in either the Cmax or t max values between single and repeated administration. Following both single and repeated administration, the inter-individual variation in plasma levels of both lidocaine and prilocaine was high, in both males and females and at all dose levels of EMLA. The plasma levels of prilocaine were considerably lower than those of lidocaine.

At the highest dose level (12.5 mg/kg), the plasma levels ranged as follows;
114-238 ng/mL (lidocaine) and 31-88 ng/mL (prilocaine) in males, and 89-1 78 ng/mL (lidocaine) 44-60 ng/mL (prilocaine) in females.

Elimination of both lidocaine and prilocaine from blood was rapid; 24 hours after treatment, the levels of both compounds were below the limit of detection (10 ng/mL). [Vol. 44.1, pp.42-45.]

SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES

The sponsor has provided fourteen clinical studies in support of the use of EMLA Cream in genital mucous membranes. Twelve of the studies involved single-dose applications of EMLA Cream 5% that are the bulk of the evidence in this document. One study (81P029) involved EMLA Cream 2%, and one study (89LiO2) involved repeated dosing. All fourteen clinical studies are presented in Reviewer's Table 3 in a grid format. The studies are displayed in rows according to their study design and in columns according to the clinical indication, which they either establish or support.

Three studies (86EM07, 86EM04:1, and 83P026:2) are submitted as pivotal studies in support of the efficacy of EMLA Cream 5%, applied for five to ten minutes, to provide topical anesthesia for minor surgical procedures on genital mucous membranes. Four additional controlled studies (84EM07, EM9404, 84EM06 and 86EM 12) and two open uncontrolled studies (84EM 11 and86EM04 Part II) had exposure times that were longer than ten minutes. The results of these studies are submitted in support of the selection of five to ten minutes as the most efficacious exposure time of EMLA Cream 5% for analgesia of genital mucous membranes

Two publications are presented to provide information on the duration of anesthesia and the anesthetic efficacy for procedures involving the cervix uteri. The first publication (X3, Van Der Burght,et al, 1993), assessed the duration of anesthesia of the genital mucous membranes after 5, 10 and 20 minutes' EMLA treatment. This was an open label, cross-over study in 12 healthy female volunteers. The second publication (X4, Stigliano, et al, 1997), was an open label cross over study in 88 healthy female volunteers to evaluate the efficacy of a 10-minute EMLA treatment of the cervix for hysteroscopy.

Study 90EM11, which is a randomized, double blind, single center, parallel group trial in 44

adult female patients (21 exposed to EMLA), is submitted as the only pivotal study in support of the efficacy of EMLA Cream 5%, applied for five to ten minutes, as an adjunct for infiltration of genital mucous membranes.

The sponsor has also provided 4 supportive studies, listed as "Other Indications" in Reviewer's Table 3, for the two indications that are requested in this supplement. These studies evaluated the use of EMLA Cream either with 1) a different concentration of 2% instead of 5% (81P029) or with 2) a different dose schedule (86EM12) that included a "top-up" dose after 50 minutes. or in 3) other clinical conditions such as IUD insertion (84EM12), vacuum abortion (83P036), and recurrent genital herpes (89LiO2) that involved exposure to genital mucous membranes. These four studies are provided to give additional supportive efficacy and safety data for the use of EMLA on genital mucous membranes.[Vol.44.9, pp.9-10.]

It should be noted that Study 84EM12, while not a pivotal study, was a randomized, double blind trial and was used in this reviewer's determination of the Data Integrity. [See Section 7.1.1, p.20 of this review.]

SECTION 5.1 PRIMARY SOURCE DATA

Section 5.1.1 *Study Type and Design/Patient Enumeration*

Reviewer's Table 3: Categorization of studies by study design and clinical significance*

	ISE CATEGORIES (STUDY INDICATION)			
ISS. STUDY CATEGORIES (STUDY DESIGN)	**Superficial Minor Surgery**		**Adjunct to Infiltration**	**Other Indications**
	(Establishes 5-10 min Exposure)	**(Supports 5-10 min Exposure)**		
lacebo-Controlled	86EM07	84EM07	90EM11	84EM12
Active-Controlled		84EM06 EM9404		
Application Time-Response	86EM04:Part 1 83P026	86EM12		
Uncontrolled		86EM04:Part. 2 84EM11		83p036
Different Concentration or Application Schedule				89Li02 81P029
Publications		X3 X4		

* The studies are designated by their protocol numbers. Studies are displayed horizontally according to their study design and vertically according to the clinical indication, which they either establish or support in the sNDA. [Vol. 44.9, p.11.]

On the following five pages are tables of all clinical; studies submitted by the sponsor for this supplement. (reviewer's Tables 4, 5, 6, 7,and 8)

Placebo controlled studies

Study Code Report No.	Vol/ Page	Title	Investigator(s) /Country	Trial Design	Literature Citation	Started/ Completed	Age Range (mean)	M/F	Treatment Groups Application Times	No. of Patients		
										Enrolled	Exposed	Evaluable
Indication: Local anesthesia for minor surgical procedures												
86EM07 802-10 AC 062-1	Vol 3 Page 7	Local Anaesthesia with EMLA Cream for Laser Treatment of Condylomata Acuminata in Women. A Double-Blind Comparison with Placebo to Evaluate the Time of Onset and Duration of Anaesthesia of the Genital Mucosa	Rylander Sjöberg *Sweden*	Randomized, double-blind, parallel group, single center	Rylander E, et al., Obstet Gynecol 1990;75: 302-6	06/86 - 08/87	18-55 (26) 17-45 (25)	0/60 0/20	EMLA Cream (5%) 1- 75 minutes Placebo cream 1-75 minutes	60 20	60 20	59* 20
84EM07 802-10 AC036-1	Vol 3 Page 92	A Study of EMLA, a Lidocaine-Prilocaine Cream, Used as a Topical Anaesthetic for Cervical Curettage. A Double-Blind, Randomised Comparison with Placebo	Holmgren Nilsson *Sweden*	Randomized, double-blind, parallel group, single center	None	10/84 - 09/85	22-56 (32) 21-55 (34)	0/30 0/30	EMLA Cream (5%) in vaginal fornices for 20 min Placebo cream 20 min	30 30	30 30	30 30
Indication: An adjunct to local infiltration anesthesia in genital mucous membranes												
90EM11 62-18/051-18	Vol 3 Page 174	A Double-Blind Study on the Topical Analgesia Experienced with EMLA Cream as a Premedication to Infiltration Anaesthesia in the Genital Mucosa of Women	Zilbert *Canada*	Randomized, double-blind, parallel group, single center	Zilbert AW, et al, Nova Scotia Med Journal, 1993;72(6): 210-211	02/91 - 04/92	19-63 (37) 18-76 (34)	0/22 0/23	EMLA Cream (5%) 6-10 min Placebo 6-9 min	22** 23	21 23	21 23

* 59 patients were evaluable for efficacy analysis of VAS pain scores, whereas 58 patients were evaluable for "need for supplementary anesthesia".

** Patient 121 was excluded before exposure to study drug as she had taken an analgesic within 4 hours of the procedure.

Application time-response studies

Study Code Report No.	Vol/ Page	Title	Investigator(s) Country	Trial Design	Literature Citation	Started/ Completed	Age Range (mean)	M/F	Treatment Groups Application Times	No. of Patients		
										Enrolled	Exposed	Evaluable
86EM04 Part I 802-10 AC 064-1	Vol 4 Page 1	Local Anaesthesia with EMLA Cream for Cautery of Condylomata Acuminata of the Genital Mucosa in Women - Effect of Application Time	Ljunghall *Sweden*	Open-label, single center Pilot study: each subject acting as own control to determine the anesthetic onset time Main study: allocation to 10, 15 or 20 min treatment with EMLA	Ljunghall K, et al. Acta Derm Venereol 1989;69: 362-65	06/86 - 04/87	18-25 (22)	0/10	Pilot study: EMLA Cream (5%) 5 - 10 min Main study: EMLA Cream for	10	10	10
							18-25 (22)	0/42	10 min	13	13	12
							18-26 (22)		15 min	19	19	18
							18-28 (21)		20 min	10	10	10
83-P026 802-10 AC025-3	Vol 4 Page 70	An Open Study on a 5% Lidocaine-Prilocaine Cream, EMLA, Used as Topical Anaesthesia for Cervical Curettage	Kull Holm *Sweden*	Open-label, single center allocation to 3 groups of active EMLA treatment	None	12/83 - 08/84			EMLA Cream (5%) in vaginal fornices:			
							21-40 (30)	0/8	10 min	8	8	8
							18-40 (29)	0/21	20 min	21	21	21
							18-47 (31)	0/10	60 min	10	10	10
86EM12* 802-540-LC-0008	Vol 4 Page 150	Diathermy Treatment of Condylomata in Females with EMLA 5% Cream	Tronstad *Sweden*	Open label, randomized, comparative, parallel group. Multicenter	None	09/86 - 06/88	17-51 (25)	0/19	EMLA Cream (5%) 60 min	19	19**	19**
							18-55 (28)	0/20	EMLA Cream (5%) + 5g EMLA Cream (5%) "top up" 50 min after application	20	20**	20**
							18-57 (32)	0/3	Infiltration only (mepivacaine/ adrenaline)	3	3	0

* Because of poor enrollment, an amendment was written to this protocol to cancel the infiltration treatment group. The study was thus reclassified as an application time-response study.

** In total, 33 patients in Study 86EM12 were exposed to EMLA on mucous membranes.

Active Controlled studies

Study Code Report No.	Vol/ Page	Title	Investigator(s) /Country	Trial Design	Literature Citation	Started/ Completed	Age Range (mean)	M/F	Treatment Groups Application Times	No. of Patients		
										Enrolled	Exposed	Evaluable
84EM06 802-10 AC 033-1	Vol 4 Page 213	A Comparison of EMLA Cream 5% and Mepivacaine Adrenaline 1% as Anaesthetic Agents for Cervical Curettage in an Open Randomized Study	Kull Lanner *Sweden*	Open label, randomized, comparative, parallel group, single center	None	10/84 - 05/85	19-38 (26.5) 19-38 (26.5)	0/30 0/30	EMLA Cream (5%) in vaginal fornices for 20 min Paracervical block w/mepivacaine (1%)	30 30	30 30	26 30
EM9404 EM9404	Vol 5 Page 1	Comparative Study of Topical Analgesia with EMLA® 5% Cream and Anesthesia by Infiltration of Lidocaine for Biopsies of the Genital Mucosa	Lessana-Leibowitch, Dubertret, Guillet, Morel, *France*	Open label, randomized, parallel group, multicenter	Droualt et al. Ann. Dermatol. Venereol. 1997;124: 448-451.	02/94 - 11/94	22 - 73 (47.1) 18 - 81 (48.4)	9/22 8/24	EMLA Cream (5%) 7 - 12 min Lidocaine (1%)	31 32	31* 32*	30* 31*

* In Study EM9404, 22 and 24 patients were treated on mucous membranes in the EMLA and the lidocaine groups, respectively.

Uncontrolled studies

Study Code Report No.	Vol/ Page	Title	Investigator(s) /Country	Trial Design	Publication	Started/ Completed	Age Range (mean)	M/F	Treatment Groups Application Times	No. of Patients		
										Enrolled	Exposed	Evaluable
84EM11 802-10 AC 038	Vol 6 Page 2	Topical Anaesthesia with a Local Anaesthetic Cream (EMLA®) for Cautery of Genital Warts	Hallen Ljunghall Wallin *Sweden*	Open-label, single center	Hallen et al. Genitourin Med 1987;63: 316-9	11/84 - 12/85	Female 16-41 (21) Male: 17-59 (27)	57/ 51	EMLA Cream (5%) 30 -105 min 20 - 70 min	108 51 F 57 M	108 51* F 57* M	108 51* F 57* M
86EM04 Part II 802-540 LC0009-02	Vol 6 Page 93	A Discontinued Clinical Study of the Thermocautery of Condylomata Located on Genital Skin in Women Under Local Anaesthesia with EMLA Cream 5%	Ljunghall *Sweden*	Open-label, single center randomized, parallel groups	None	04/87 - 05/89	20 - 39 (25)	0/13	EMLA Cream (5%) 60 min or 90 min on genital skin 10 min on genital mucosa	13	13**	13**

* Includes both patients treated on skin and patients treated on mucosa. In Study 84EM11, 43 women and 7 men were treated on mucous membranes.

** Includes both patients treated on skin and patients treated on mucosa. In Study 86EM04 Part II, 4 patients were treated on mucous membranes.

Other indications/formulations

Study Code Report No.	Vol/ Page	Title	Investigator(s) /Country	Trial Design	Publication	Started/ Completed	Age Range (mean)	M/F	Treatment Groups Application Times	No. of Patients		
										Enrolled	Exposed	Evaluable
84EM12 802-10 AC043-1	Vol 6 Page 140	A Study of EMLA Cream 5% for Use as a Topical Anaesthetic for Insertion of IUD. A Double-Blind Randomized Comparison with Placebo	Barden, Loudon *UK*	Randomized, double-blind, parallel group, single center	None	08/85 - 05/86	17-37 (28) 18-44 (31)	0/23 0/21	EMLA Cream (5%) 11-21 min Placebo, 11-19 min	23 23*	23 21	23 20
83P036 802-10 AC 024-2	Vol 6 Page 185	An Open Study of EMLA, a Lidocaine-Prilocaine Cream, Used as Topical Anaesthetic for Prevention of Pain During Vacuum Abortion	Nilsson *Sweden*	Open-label, single center	None	12/83 - 08/84	22-38 (29)	0/20	EMLA Cream (5%): 10 min in fornices + paracervical injections of 0.9% saline (pilot study) 10-20 min in fornices In fornices and cervical canal for: 20 min 60 min	 2 11 4 3	 2 11 4 3	 2 11 4 3
81P029 802-10 AC 017-1	Vol 6 Page 264	Study on a Eutectic Lidocaine-Prilocaine Cream (EMLA) Used as Amesthetic Agent for Cervical Curettage and Vacuum Abortions	Kull *Sweden*	Open label, uncontrolled, single center	None	04/82 - 07/82	19-51 (33)	0/31	EMLA Cream (2%) in vaginal fornices for 6-25 min in the cervical curettage group and 10-60 min in the abortion group	31	31	31
89LI02 802-540-LC-0023-01	Vol 7 Page 1	A Clinical Study of the Effects of EMLA Cream 5% on Cure and Relief of Symptoms from Episodes of Recurrent Genital Herpes Simplex Infections	Hallén Lind *Sweden*	Randomized, double-blind, parallel group, multicenter	None	02/90 - 12/91	25-66 (34) 21-55 (33)	9/14 14/7	EMLA Cream (5%) or placebo cream in the prepudendal cavity of introitus vaginae three times daily for three days (no removal of cream, thus no application time)	} 93	23* 21*	23 21

* Study 84EM12: for two patients randomized to the placebo group, tubes with EMLA/placebo were mixed up; therefore, it is not known whether the patients received EMLA or placebo.

** Includes both patients treated on skin and patients treated on mucosa. In Study 89LI02, 4 and 2 patients in the EMLA and placebo groups (respectively) were treated on mucous membranes.

[Vol.44.3, pp.2-5.]

SECTION 5.1.2 DEMOGRAPHICS

This paragraph and the sponsor's Table 5 (Reviewer's Table 9) on the next page summarize the patient demographics and baseline characteristics of all female patients treated in the twelve studies which evaluated single application doses of EMLA Cream 5% or placebo or an active control on mucous membranes. The median age of patients in the studies ranged from 22 to 35 years, with a minimum of 16 and a maximum of 80 years. Older patients, median 47-48 years, were recruited in a study of genital biopsies (EM9404), reflecting the indication studied. The overall median height of patients was 65 cm and the median weight was 58 kg. The treatment groups were comparable. [Vol. 44.9, pp.117-118.]

Table 5: Age, height and weight of female patients treated with single doses of EMLA Cream 5% on mucous membranes

	Placebo-controlled		Active-controlled		Appl. time-response	Uncontrolled	All
	EMLA 5%	Placebo	EMLA 5%	Injection	EMLA 5%	EMLA 5%	EMLA 5%
Age (years)							
n	135	94	52	54	124	67	378
Missing (n)	0	0	0	0	0	0	0
Mean	30	32	37	38	26	24	28
Median	27	30	35	31	23	22	25
Minimum	17	17	19	18	18	16	16
Maximum	63	76	73	80	55	38	73
Height (cm)							
n	54	50	30	30	39	20	143
Missing (n)	81	44	22	24	85	47	235
Mean	165	166	165	166	166	167	165
Median	164	168	165	165	167	168	165
Minimum	153	150	153	157	156	159	153
Maximum	180	179	173	178	181	176	181
Weight (kg)							
n	54	50	30	30	39	20	143
Missing (n)	81	44	22	24	85	47	235
Mean	58	61	61	62	62	61	60
Median	56	58	60	59	61	58	58
Minimum	48	43	45	49	39	54	39
Maximum	78	114	95	100	95	73	95

Data Sources: Studies 86EM07, 84EM07, 90EM11, 84EM12, EM9404, 84EM06, 86EM04:1, 86EM04:2, 83P026, 86EM12, 84EM11, 83P036

Reviewer's Table 9.[Vol. 44.9, p.118.]

Section 5.1.3 Extent Of Exposure

The integrated safety data set (ISS) consisted of 526 evaluable patients, of whom 378 were exposed to EMLA. Due to the different application schedule and different concentration of EMLA used in studies 89Li02 and 81P029, these two studies were not included in the integrated safety data set. The number of evaluable patients included in the EMLA 5% single dose integrated summary of efficacy (ISE) was 522, of whom 376 were exposed to EMLA.

The sponsor explains differences between the ISS and the ISE in number of patients as due to the following:

- in the efficacy data 7 men were included
- 16 patients were excluded from the efficacy data set compared to 6 patients from the safety data set
- in the integrated safety data set both exposures of the patient who was enrolled twice are included (84EM07)

[Vol.44.9, pp. 113, 115.]

Table 4: Safety data set for EMLA Cream 5%, placebo and control treatment exposure (n=526) on genital mucous membranes in females (number of patients per study and treatment group)

ISS CATEGORIES (STUDY DESIGN)	ISE CATEGORIES (STUDY INDICATION)					INTEGRATED SAFETY DATA SET (totals)		
	Superficial Minor Surgical Procedures (Establishes 5-10 min Exposure)		Superficial Minor Surgical Procedures (Supports 5-10 min Exposure)		Adjunct to Infiltration	Other Indications	EMLA	Placebo	Control
Placebo-Controlled	86EM07		84EM07		90EM11	84EM12			
EMLA	60		31		21	23	135		
Placebo	20		30		23	21		94	
Active-Controlled			EM9404*	84EM06					
EMLA			22	30			52		
Control			24	30					54
Application Time-Response	86EM04:1	83P026	86EM12**						
EMLA	52	39	33				124		
Uncontrolled			86EM04:2***	84EM11****		83P036			
EMLA			4	43		20	67		
Different Concentration or Application Schedule						89Li02*****	81P029******		
EMLA						4	31		
Placebo						2			

* 9 EMLA patients and 8 control patients were excluded from the integrated safety data set because their exposure was not on mucous membranes.

** 6 EMLA patients were excluded from the integrated safety data set because their exposure was not on mucous membranes.

*** 9 EMLA patients were excluded from the integrated safety data set because their exposure was not on mucous membranes.

**** 58 female EMLA patients were excluded from the integrated safety data set because their exposure was not on mucous membranes. In addition to the 43 female patients, seven men had EMLA applied on mucosa; these are not included in the integrated data set, but anlayzed separately.

***** The entire enrollment (44 evaluable patients) was excluded from the integrated safety data set because they received repeated applications of the drug. However, six of the patients received EMLA on mucous membranes and the results for these patients are presented separately (see Section 6.7).

****** The entire enrollment of this study (31 patients) was excluded from the integrated safety data set because they were dosed with 2% EMLA. However, all 31 patients were exposed to EMLA on genital mucous membranes; the results from this study are presented separately (Section 6.7).

Reviewer's Table 10. [Vol. 44.9, p.116.]

SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS

The sponsor stated that the active ingredients of EMLA® cream, lidocaine and prilocaine, are both well characterized with respect to pharmacokinetics. Moreover, in view of EMLA® being intended for topical use for local effect only, a full pharmacokinetic program was not thought necessary. Plasma concentrations have, however, been monitored to ascertain safety in four clinical studies (1-4), where EMLA®cream 5% or 2% was applied as a topical anesthetic to genital skin in males and to genital mucous membranes in females.

The doses used in females were 5-10 g of EMLA® 5 % corresponding to 125-250mg each of lidocaine and prilocaine base and, in one study, 5 g of EMLA® 2 %, which equals 50 mg each of lidocaine and prilocaine base. One g EMLA® equals one milliliter. Concentrations obtained with application times of about 10, 15, 20 and 60 minutes were studied.

The highest individual C_{max} values observed were 641 ng/ml for lidocaine and 346 ng/ml for prilocaine, originating from two patients in whom 10 g of EMLA® 5 % was applied for 69 minutes bilaterally in the vaginal fornices and for 24 minutes in both the cervical canal and fornices, respectively.

For both lidocaine and prilocaine, individual C_{max} and t_{max} values were erratic, reflecting the impact of the variety of factors likely to govern absorption, such as application time, dose applied per area, and the nature of the application site. Also the blood sampling schedules had an influence on the obtained C_{max} and t_{max} values, due to the sparsity and spacing of sampling points.

The systemic bioavailability was assessed after the application of 0.3-3.3 g of cream to genital skin in males. These doses correspond to 7.5-82.5 mg each of lidocaine and prilocaine base. The bioavailability (expressed as mean $\pm$SD) was low, 14 $\pm$10 % for lidocaine and 6 $\pm$3 % for

prilocaine. The individual estimates are impaired, especially at low doses owing to methodological aspects, such as poor precision in estimating the amount of cream applied and the large residual plasma AUCs (the extrapolated AUC from the last sampling time to infinity).

The interindividual variability was substantial, bioavailability values being in the range [redacted] for lidocaine and [redacted] for prilocaine. This is due, at least in part, ii) physiological variability per se, but is likely to be inflated by the methodological considerations present.

When comparing C_{max} levels after application to genital skin vs mucosa, values more than twice as high were obtained in the latter case, even when differences in doses were taken into consideration. The sponsor goes on to state that it is reasonable to assume that the explanation for the higher dose-corrected C_{max} values is the more favorable absorption properties of mucous membranes, such as the absence of stratum corneum and high blood perfusion Hence higher bioavailability is to be expected for application to mucosa given the limited application times.

In summary, the peak plasma concentrations of lidocaine and prilocaine obtained after the application of 0.3-10 g (7.5-250 mg each of lidocaine and prilocaine base) EMLA® 5 % to genital skin or mucosa were approximately one-tenth or less of those considered likely to cause systemic toxicity.

The occurrence of systemic CNS toxicity from lidocaine and prilocaine is related to peak plasma levels of the anesthetics. Initial signs of toxicity such as lightheadedness and dizziness have been reported at venous plasma levels of either anesthetic above 5000-6000 ng/ml.

The pharmacokinetic objective of the clinical studies included in this section has been to assess safety in terms of the maximum plasma concentration (C_{max}) of lidocaine and prilocaine resulting from the application of EMLA® cream 2 % or 5 % to genital skin or mucous membranes in adults (1-4). The time (t_{max}) to reach C_{max} was also assessed. In one of the studies, the primary objective was to investigate the systemic bioavailability of lidocaine and prilocaine. Pharmacokinetic parameter values are presented as mean $\pm$SD.

The recommended dose of EMLA® cream 5% is 5-10 g and the recommended application time on mucous membranes for optimal anesthetic efficacy is 5- 10 minutes; however, for safety reasons, plasma levels following prolonged exposures of up to approx. 60 minutes have been studied.
[Vol. 44.2, pp. 3-4.]

Summarized outlines of all the pharmacokinetic studies are given on the following page:

Table 1: All pharmacokinetic studies

Ref. No.	Study code Report No. Investigators	Study Design	Treatment Dose	Number of patients Enr	Number of patients Exp	Age Range	M/F	Publi-cation	Location Report CRFs (Vol/Pg)
1	83-P026 802-10 AC025-3 B Kull Dept. of Obstetrics & Gynecology Falu Hospital, Falun, Sweden	Open, non-randomized, application-time-response for cervical curettage in out patients with cervical intraepithelial neoplasia Premediction by 5 mg diazepam in 3 patients (20-min group)	10 g EMLA 5% cream of pH 8.5 (12 pats) or 9.5 (27 pats) was applied vaginally in the lateral fornices (5 g on either side) either for 10 min (8 patients) 20 min (21 patients) or 60 min (10 patients)	39	39	18-47	0/39	None	
2	83-P036 802-10 AC 024-2 Bo A Nilsson Dept. of Obstetrics & Gynecology Södersjukhuset, Stockholm, Sweden	Open, non-randomized, EMLA as topical anesthesia for vacuum abortion in out patients Premedication with 10 mg oxicone, 0.4 mg scopolamine sc or im, and 2.5 - 5 mg diazepam iv	10 g EMLA 5% cream applied either in the vaginal fornices for 10 min (n=6) in the vaginal fornices for 20 min (n=7) in the vaginal fornices and the cervical canal for 20 min (n=4) in the vaginal fornices and the cervical canal for 60 min (n=3)	20	20	22-38	0/20	None	
3	93-EML-18 (p. II) M Alan Menter Texas Dermatology Associates., Dallas	Open study in males for cryotherapy of genital warts. Cross over bioavailability comparison with iv lidocaine and prilocaine	0.9 g EMLA 5% cream (range 0.2 to 3.3 g) applied to the genital skin of the shaft of the penis (n=19) or the glans penis (n=1) 10 mg iv lidocaine and 10 mg iv prilocaine each over a period of 1 minute	20	20	18-65	21/0	J Am Acad Dermatol 1997;37:96 -100	
4	81-P029 802-10 AC017-1 B Kull Dept. of Obstetrics & Gynecology Falu Hospital Falun, Sweden	Open, non-randomized, EMLA used as a topical anesthetic for cervical curettage or vacuum abortion in out patients	5 g EMLA 2% cream applied in the vaginal fornices and in the cervical canal Plasma samples taken after application times of 10 - 20 minutes in 10 patients undergoing cervical curettage and biopsy	31	31	19-51	0/31	None	

Reviewer's Table 11. [Vol. 44.2 p. 10.]

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 OVERVIEW OF CLINICAL STUDIES

The sponsor has stated as previously noted in Section 5.0 of this document, that three studies (86EM07, 86EM04:1,and 83P026:2) are being submitted as pivotal studies in support of the efficacy of EMLA Cream 5%, applied for five to ten minutes, to provide topical anesthesia for minor surgical procedures on genital mucous membranes. One study (90EM 11) is being submitted as a pivotal study in support of the efficacy of EMLA Cream 5%, applied for five to ten minutes, as an adjunct for infiltration of genital mucous membranes.

It should be noted that Study86EM04: 1 and Study 83P026: 2 are open label studies. Study 83P026:2 was originally a double-blind randomized comparison trial of 2% vs 5% EMLA but, after approximately 10 patients, was changed to an open label design. Study 84EM12, will be looked at in the Data Integrity section below, is a placebo-controlled study but is done for an indication not applied for in this supplement (placement of an IUD). The sponsor has provided two trials (90EM11 and 86EM07) that appear to be adequate and well controlled trials

Study 86EM07, that the sponsor considers a supportive study, is a randomized, double-blind, placebo-controlled , parallel group , single-center study of EMLA for local anesthesia during laser treatment of condylomata acuminata in adult women. Of the 80 female patients in the trial, 60 received 5 g of EMLA and 20 received 5 g of placebo cream. The second study, Study 86EM04 part I is an open-label, single center study of the local anesthetic effects of EMLA for cautery of condylomata acuminata of the genital mucosa of women (the effect of application time). In the pilot portion of the study, each subject acts as their own control to determine anesthetic onset time. Forceps pinches are applied before and after cream (5-10g) and every one to two minutes thereafter until pain score was close to zero or pain score had no decreased since last pinch. In the main study, groups are allocated to 10, 15 and 20 minutes after application (5g) before surgery is attempted. There are 10 female patients in the pilot study

and 42 female patients in the main study. The third study, Study 83PO26 is an open-label, single center, allocation of 3 groups using EMLA as topical anesthesia for cervical curettage. Application times are 10, 20, and 60 minutes. This is a PK study in which venous plasma levels of lidocaine and prilocaine are determined in patients who had EMLA (10 mL) applied for 60 minutes. There are a total of 39 female patients in the study.

The sponsor feels that Study 90EM11 supports their claim for the indication of adjunct for local infiltration anesthesia in genital mucous membranes. This study is a randomized, double-blind, placebo-controlled, parallel group single center study of EMLA as topical analgesia pre-medication for infiltration anesthesia in the genital mucosa of women. There are two groups, one group gets EMLA cream (5 g), and the other gets a placebo cream (5g),.45 female patients (23 on EMLA)

Study 81PO29 studied EMLA Cream at 2% concentration which is not the concentration being proposed in this supplement. Study 89LiO2 studies recurrent use. This application is for one time use before injection and/or minor surgical procedures. Study 83PO36 is for vacuum abortion, which is not a minor surgical procedure and not in the sponsor's proposed labeling. Study 86EM04, Part II was discontinued. These studies, for the reasons, mentioned above will not be included in a discussion of the efficacy results.

The remaining 6 studies may be considered supporting studies. As also stated previously in Section 5.0 of this document, the sponsor has submitted two publications. These publications provide information on the duration of anesthesia and the anesthetic efficacy for procedures involving the cervix uteri. The first publication assessed the duration of anesthesia of the genital mucous membranes after 5, 10 and 20 minutes' EMLA treatment The second publication evaluated the efficacy of a 1minute EMLA treatment of the cervix for hysteroscopy.

After consultation and discussion with Dr. Shinja Kim, Biopharm Reviewer, it was felt that the sponsor's designated pivotal trials would be acceptable to review for efficacy, based on the fact that almost all of the pivotal trial patients received the currently marketed formulation. All the submitted trials (using both marketed and older formulations) could be integrated for the safety

review providing the sponsor submits and bridging or bioequivalence study to show the formulations are equivalent.

Section 7.1.1 Data Integrity

No investigation of the trial sites was performed

Because there were no reports of patient deaths, serious adverse events or discontinuations due to adverse events, the sponsor did not provide any Case Report Forms with the original submission of this supplement. On consultation with Dr. Sue Jane Wang, Biostat Reviewer, it was decided to request that the sponsor provide Case Report Forms for approximately 10% of patients, randomly selected by Dr. Wang, from each of 4 double-blinded trials (84EM07, 84EM12, 86EM07, and 90EM11) in order to conduct a data integrity evaluation. Dr. Wang and this reviewer performed a comparison of the Case Report Forms to the data line listings. It should be noted that the results of this sampling showed that, with regard to treatment assignment, data was either missing, the same code placed on all the forms in one study, or coded as "A" or "B". It is unclear how the assignments of "A" or "B", the use of the same code number for each patient, or the blank treatment assignment fields were translated into EMLA or placebo in the data line listings. On December 21, 1999, the sponsor provided clarification regarding the issue of treatment assignment. When the data was pooled, the data manager accidentally reversed the data values. On checking the treatment against the randomization list, it was found that they do correctly match. Although there is a remote possibility we are missing something, this reviewer feels we can accept this reversal of data as a mistake. [See Biostat review.]

Section 7.1.2 Financial Disclosure

On December 23, 1999, the sponsor submitted Certification: Financial Interests and Arrangements of Clinical Investigators form 3454. The sponsor states that none on the investigators have entered into any financial arrangement with the sponsor, "whereby value of compensation to the investigator could be affected by the outcome of the study as defined in 21

CFR 54.2(a).". As a result of this statement, Disclosure: Financial Interests and Arrangements of Clinical Investigators form 3455 does not have to be submitted.

SECTION 7. SUMMARY OF STUDIES PERTINENT TO EFFICACY:

SECTION 7.2.1 *STUDY 86EM07*

Section 7.2.1.1Protocol Synopsis:

Title: Laser treatment of condylomata in females under local anesthesia with EMLA® Cream. A placebo controlled trial to determine the minimum effective application time of the cream./

Objectives: The objectives of this trial are to investigate the use of EMLA cream as local anesthesia for laser treatment of the female genital mucosa regarding:

- analgesic efficacy compared to placebo
- minimum effective application time
- any decrease in analgesic efficacy up to 75 minutes application time.

In addition, the pain from injection of any additional analgesia in the EMLA and placebo groups will be compared.

Study Design: This trial is a single center, randomized, double blind, placebo-controlled, parallel group study. Stratification will be used to obtain an even spread of application times around the expected minimal effective time of 10-20 minutes. The shortest time will be 1 minute and the longest 75 minutes. After consent to participate is obtained a sealed envelope with the randomized application time is opened. A dose of 5g cream is evenly spread over the genital mucosa down to introitus vaginae. A plastic wrapping (Glad®) will be applied to keep the cream in the desired location. Pre-medication will not be used. At the stipulated application time the cream is wiped off, the mucosa is examined for any local reactions and the patient is asked about any discomfort caused by the cream. A standardized area of 3 x 3 cm on the mucosa containing at least one condyloma is treated by the laser beam. The patient is then asked to assess the pain on a Visual Analogue Scale (VAS) and on a verbal rating scale. The number of warts is

recorded. If painful, the treatment will be stopped immediately, and pain assessments made before additional anesthesia is given. If local infiltration anesthesia is used, the pain from the additional injection will also be assessed on a VAS before completion of treatment. Any condylomas outside of the standardized area to be removed at the same occasion must be treated after the pain evaluation on the standardized area. The used method of anesthesia outside of the standardized area will be recorded. Recordings of this treatment may be made as comments on the case record form.

Pain Assessment:

The patient will be asked to assess the pain on a 100 mm visual analogue scale (VAS) with the endpoints 'no pain' and 'severe pain'. The pain will also be assessed by a verbal rating scale as 'none", "slight', "moderate" or "severe" where:

Slight pain = quite tolerable

Moderate pain = not quite tolerable

Severe pain = intolerable

analgesic efficacy compared to placebo

- minimum effective application time
- any decrease in analgesic efficacy up to 75 minutes application time.

In addition, the pain from injection of any additional analgesia in the EMLA and placebo groups will be compared.

Section 7.2.1.2 Statistical Analysis:

Endpoints will include the degree of pain from the surgery as measured on a 100 mm VAS, minimum effective application time determined by the application of the CUSUM statistical technique to the VAS scores, decrease in analgesic efficacy up to 75 minutes of application time, and pain from injection of any additional anesthesia. Verbal pain rating on a 4 point VRS categorical scale.

The comparison between the groups will be made between all placebo patients and EMLA treated patients with application times longer than the minimal effective time. VAS scores and

variances on genital mucosa, 20 patients in each group should allow detection of a difference in analgesic efficacy between placebo and EMLA with a risk level of 1% with a power of 90%. The cusum technique applied on the VAS-scores will be used to determine the minimal effective application time of EMLA cream. It may also be possible to detect an upper boundary of effective analgesia. Differences between groups will be tested by a non-parametric method. [Vol. 44.3, pp. 45-46.]

The cusum technique is described by the sponsor as a instrument for detecting shifts in trend. A prerequisite of fair comparability is that the groups compared are equally large and the successive cumulative number of patients also are equal as, for example, when there is one patient per minute application time in each group. However, in the case of discrepancy from this additive correspondence a weighting procedure has to be introduced to maintain comparability. In some 5-minute intervals in the placebo group where there are no patients at all, the overall mean 78.2 of all placebo patient scores has been used as a notional value and then multiplied by 5. This may to some extent have contributed to the rectilinearity of the placebo line. Up to 15~16 minutes following application the curves give an adequate description of a clinical reality. The lines resulting from scores from longer applications should be regarded as requiring a more cautious interpretation. [Vol. 44.3, p. 89.]

Section 7.2.1.3 Protocol Amendments:

Amendment 1 was dated February 6, 1986.It provided under the section on Anesthetic and surgical procedure

"A plastic wrapping (Glad®) ..." is changed to "A plastic wrapping (Glad®or Tegaderm®). It also provided under the section on Laser treatment "The area of 3 x 3 cm will be given a power density of 600 ~/cm^2 with an intermittent pulse of 0.5 seconds." is changed to. "pulse of 0.2 seconds". These modifications are agreed upon before any patient has been included in the trial.

Amendment 2 was dated February 17, 1987. It provided under the section Anesthetic and surgical procedure for the following addition: If EMLA® cream is given as additional analgesia, the pain from the continued laser treatment will be evaluated. This will be recorded in the patient

record form where otherwise the pain from the additional injection would have been recorded. The "VAS^2" is then changed to "VAS^3" [Vol. 44.3, pp. 51-52.]

Section 7.2.1.4 Conduct of Study:

Subject Demographic and Baseline Data

Eighty women aged 17-55 and scheduled for out patient laser treatment of condylomata on the genital mucosa (of the vulva) were to be included in the trial. Exclusion criteria were pregnancy, allergy to local anesthetics of the amide type and participation in any concomitant trial of other drugs. [Vol. 44.3, pp. 13-14.]

The ethnic origin of the patients was not recorded on the case report forms. The patient list kept at the clinic, however, did show that all the patients who entered the trial were caucasians. [Vol. 44.3, p. 52.]

On the following page is Reviewer's Table 12 giving the age of the patients and location of the warts:

The treatment groups were comparable with regard to both age and location of the test area.

	EMLA (n=60)	Placebo (n=20)
Age		
(median, range)	22.5 (18-55)	22.5 (17-45)
Location of warts		
(No. of patients)		
Vestibule	23	7
Labia minora	28	16
" " , meatus	1	-
Labia majora, interior	19	3

Reviewer's Table 12. The patients' age and the location of the test (3 x 3 cm) area. Although patients were required to be aged 18 or older, one 17-year-old woman with excessive condylomata was included as the anesthetic method was considered particularly appropriate. [Vol. 44.3, p. 18.]

Reviewer's Table 12A. PATIENT DISPOSITION

	EMLA	PLACEBO
Total Patients Randomized	60	20
Patients Evaluable for Efficacy (Note: one patient was excluded because she has no warts on mucosa but on genital skin). A second patient experienced pain, treatment was interrupted, and no additional analgesia given but pt. Still included in pain eval.	59	20
Protocol Violation* See Below	*	*

* One of the investigators translated the VAS scores from patients 1-22 onto the VRS herself instead on asking the patients. These patients have been excluded from analysis of this variable.

PROTOCOL DEVIATIONS

Major Protocol Deviations

Two patients in the EMLA group were excluded from the efficacy analysis before the code was broken: one woman had no warts on the mucosa but on the skin (Pat. No. 1), another patient was very scared and upset over the fact that she had condylomata (Pat No. 27). (The diagnosis was made on the same occasion as the treatment.) When she experienced severe pain, the laser treatment was interrupted before complete treatment of the standard area, and hence no additional analgesia was given. This patient was therefore excluded from the evaluation of the

need for additional analgesia, but has been included in the pain evaluation. [Vol. 44.3, pp.18-19.]

Minor Protocol Deviations

The assigned tube was mixed up between two patients (pat. Nos. 12 and 13), but as they were both randomized to EMLA they were included in the analysis. The assignment of patients was started simultaneously from numbers 1 and 41 by the two investigators. After the treatment of patients 41-50 one of the investigators thought that she could tell from the appearance of the cream which cream was placebo. The appearance of this batch was found on investigation at the pharmaceutical laboratory to be slightly less viscous than the active cream. All remaining tubes were therefore exchanged for a new batch of placebo (with an increased viscosity) and for new tubes of EMLA (the same batch). The investigator noting the discrepancy had by this time treated two patients with placebo (Pat. Nos. 42 and 47), and the other investigator none. These two patients were not excluded, although their treatment was only single-blinded. In the case of patients in the EMLA group between Nos. 43 and 50, the fact that the minimal and maximal effective application times were unknown to the investigator was considered to ensure an unbiased treatment. [Vol. 44.3, p.29.]

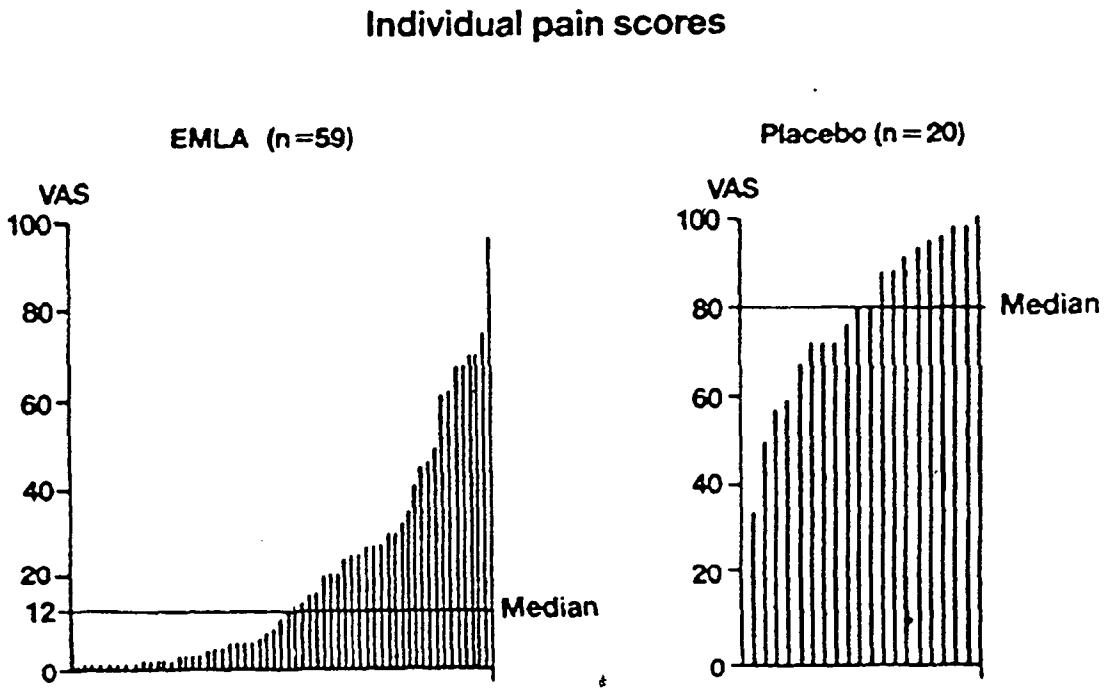
Section 7.2.1.5Sponsor's Efficacy Results:

Median pain scores were 12 in the EMLA group and 80 in the placebo group. See Reviewer's Figure 1 below. Patients treated with EMLA for 6-16 minutes showed VRS scores showed statistically less pain than placebo patients ($p < 0.01$) See reviewer's table 13. The time of onset of anesthesia of the genital mucosa was 4-5 minutes. Although clinically useful anesthesia persisted with application times of the anaesthetic cream up to approximately 30 minutes, the most effective anesthesia was achieved after 5-15 minutes application [Vol. 44.3, p.31.]
The sponsor noted that 39/42 patients allowed completion of the treatment on vulval mucosa in the EMLA group without requesting additional anesthesia. But all 20 patients in the placebo group requested additional anesthesia. [Vol. 44.9, p.30.]
Concomitant medication

Five patients in the placebo group and 26 in the EMLA group were receiving medication, mainly oral contraceptives, at the time of inclusion in the study. [Vol. 44.3, p.19.]

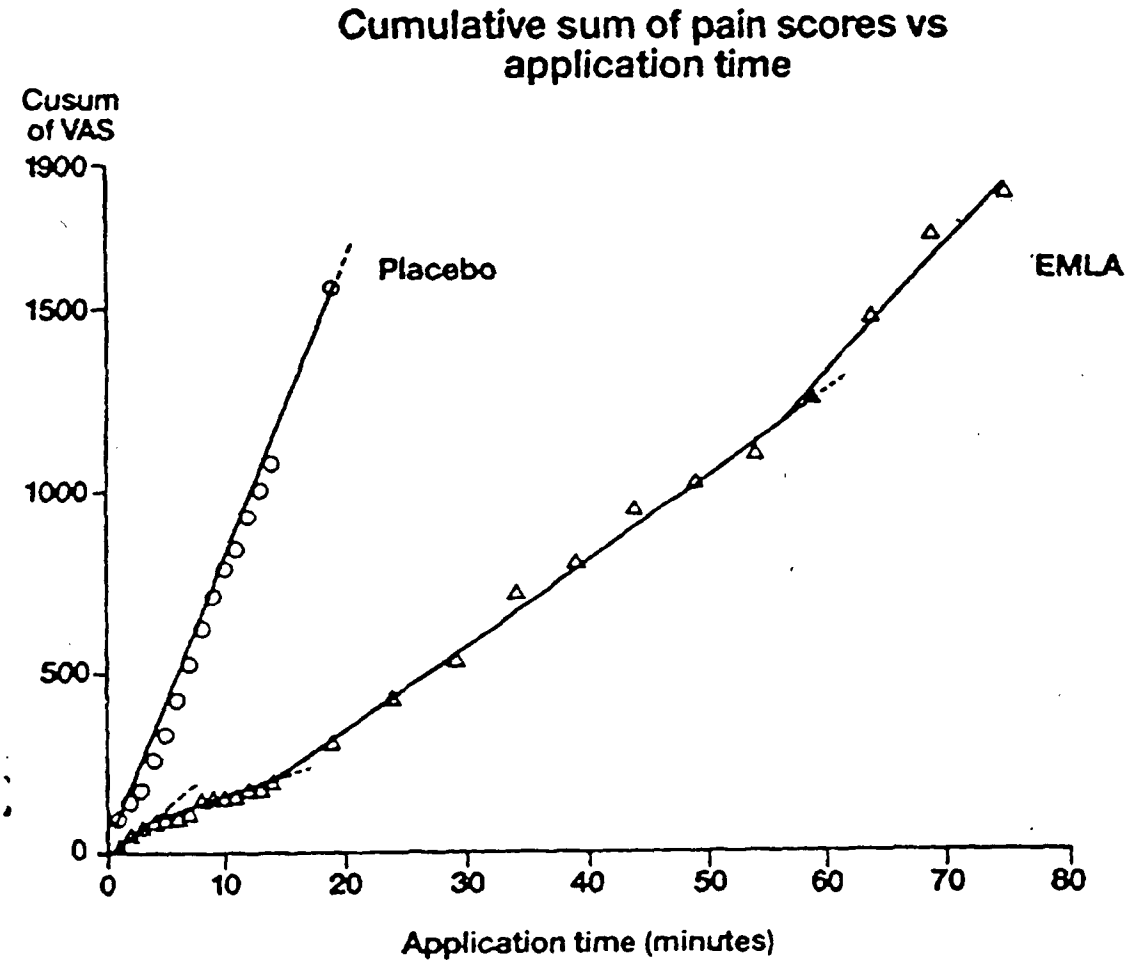
Analgesic efficacy

In the EMLA group the patients assessed the pain at 0 to 96 (median 12) on the VAS Fig. 2 on the next page). In the placebo group the patients rated the pain at 34 to 100 on the VAS (median 80).



Reviewer's Figure 1. Individual pain scores (VAS) in the treatment groups arranged in increasing magnitude of the scores. The median score is indicated by a horizontal line. [Vol. 44.3, p.20.]

The Cusum plot of the EMLA group showed that effective anesthesia was obtained after only 4-5 minutes application of the anesthetic cream (Fig. 4). There was a second shift in trend after about 15-20 minutes, and a further change after 50-60 minutes, indicating increases in pain scores.



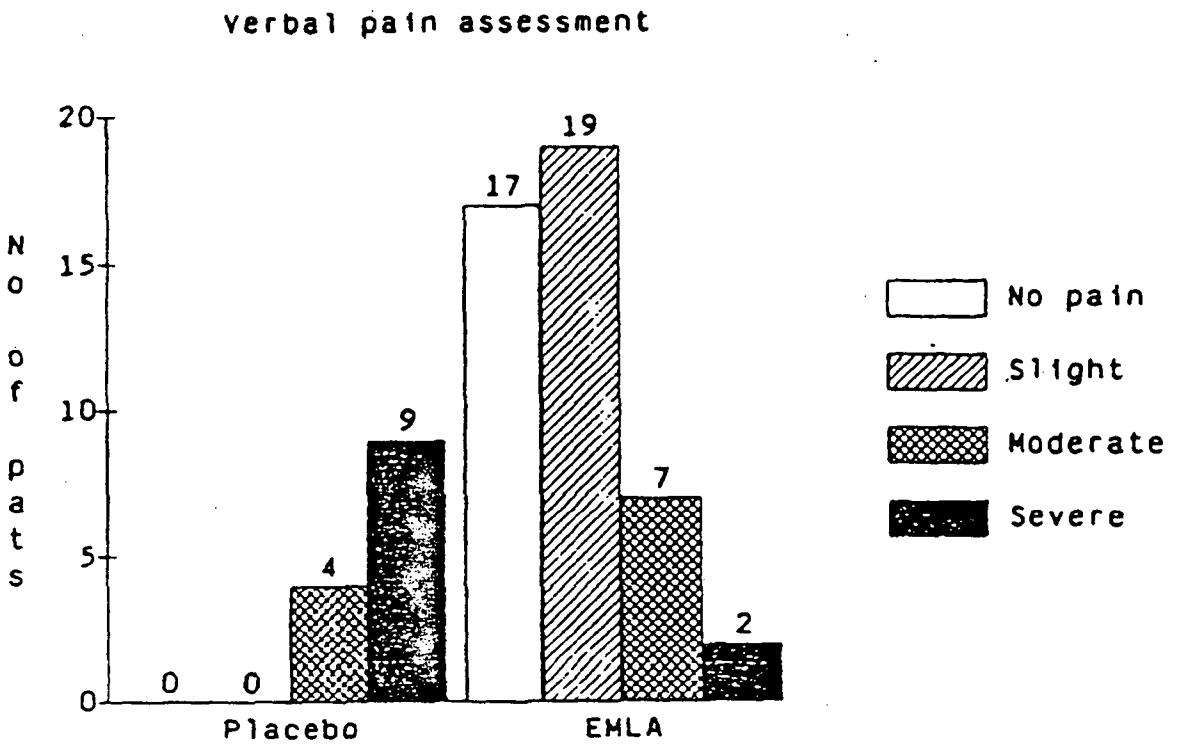
Reviewer's Figure 2. Cusum plot. The horizontal trend in the EMLA curve between 5 and 15 minutes was obscured by a VAS rating of 61 from one patient treated for 8 minutes (Patient No. 79). [Vol. 44.3, p.22.]

Verbal pain evaluation. One of the investigators translated the patients' marks on the VAS onto the four-point verbal rating scale by herself, instead of asking the patients for a verbal rating. This misunderstanding was discovered after the treatment of patients 1-22, who have been excluded from the analysis of this variable. All the remaining 13 patients in the placebo group

described the pain from the laser treatment of the test area as moderate or severe (Figure 8). The distribution of the verbal ratings against application times in the EMLA group was in accordance5 with that of the VAS scores and the need for additional analgesia

	No. of patients							
		EMLA						
		Application time (minutes)						Total
	Placebo	1-4	5-9	10-14	15-35	36-55	56-75	EMLA
No pain	0	2	5	3	5	0	2	17
Slight	0	2	4	3	0	7	3	19
Moderate	4	0	0	0	3	1	3	7
Severe	9	0	0	0	1	1	0	2
Total		4	9	6	9	9	8	45

Distribution of the verbal pain ratings among application times in the EMLA group. Patients treated with EMLA for 5-16 minutes (n=17) experienced significantly less pain than placebo-treated women ($p < 0.01$). This difference was also significant when comparing all EMLA patients with the placebo group ($p < 0.0001$).Reviewer's Table 13. [Vol. 44.3, p.37.]



Reviewer's Figure 3. Verbal pain ratings in the placebo (n=13) and EMLA (n=45) groups

[Vol.44.3, pp. 26-27.]

Pain from injection

The pain from an additional injection was assessed in seven patients, but the limited data did not allow a comparison between EMLA and placebo

Pat. No.	Appl. time (min)	Treatment group	Place of injection	Verbal pain from injection	VAS
42	26	Placebo	Test area	Severe	84
53	42	Placebo	Test area	Moderate	76
9	2	EMLA	Test area	None	N
52	17	EMLA	Test area	Moderate	68
28	11	EMLA	Mucosa	Slight	5
3	10	EMLA	Perineum	N	1
79	8	EMLA	Perineum	Moderate	77

Pain rating of injection of additional local anesthetic (N= Not assessed). Reviewer's Table 14. [Vol. 44.3, p. 37.]

Section 7.2.1.6 Reviewer's Efficacy Discussion:

The results of this study indicate that EMLA is more effective, in producing anesthesia and reducing pain caused by cautery of genital warts than placebo. The individual VAS pain scores were statistically significantly lower for EMLA than placebo ($P<0.01$). The cusum plot indicates that while pain increased over time with EMLA, it increased at a slower rate and at a reduced level compared to placebo. Verbal pain scores were also showed statistically significant difference from placebo. According to this study, effective anesthesia does appear to take place after 4-5 minutes of application. On consultation with Dr. Sue Jane Wang, Biostatistical Reviewer, it was felt that this pivotal trial was clear cut for efficacy and the CUSUM analysis only facilitated the results.

SECTION 7.2.2 *STUDY 86EM04 Part 1*

Section 7.2.2.1Protocol Synopsis:

Title: Local Anesthesia With EMLA Cream For Cautery Of Condylomata In Females Under Local Anesthesia With EMLA Cream. A Clinical Study

Objectives: The objectives of this trial are to investigate the use at EMLA cream as analgesia for cautery of mucosal condylomata in the female regarding

- correlation between analgesia to a forceps pinch and analgesia to cautery (Pilot study)
- minimum effective application time (Pilot study)
- analgesic efficacy within an interval of 10 - 20 minutes from the minimum effective time (Part I)

[Vol. 44.4, p.30.]

Study Design: This trial has an open design involving 52 female out-patients ages 18 or older (10 in the pilot study)

Pilot-study. In ten patients a dose of 5 - 10 g EMLA cream is evenly spread over the genital mucosa down to introitus vaginae. The pain from a forceps pinch is recorded before administration of the cream and then after application of the cream every five minutes until analgesia is optimal, as assessed by a Visual Analogue Scale (VAS). Optimal analgesia is considered present when the VAS score is close to zero or the VAS score is not decreased compared to the last test (not counting the test before the cream was given). When optimal analgesia is present the cream is wiped off, the mucosa examined for any local reactions and the patient is asked about any discomfort caused by the cream. Condylomas on the mucosa are removed by cautery, and the patient is asked to assess the pain on a VAS and on a verbal rating scale. In case the treatment is painful additional infiltration anesthesia will be given. The number of warts and need for supplementary analgesia is recorded. Any condylomas outside of the mucosa (on skin) to be removed at the same occasion must be treated after the pain evaluation on mucosa. The analgesic efficacy on skin will not be recorded.

Part I Each condyloma on the genital mucosa will be covered by at least 1 g of EMLA cream, a

maximum of 10 g per patient. Based on the pilot study, an application time interval of 10-20 minutes ranging from the minimal effective time will be used. If additional analgesia is required, the pain from the injection will also be evaluated. Any condylomas outside of the mucosa (on skin) to be removed at the same occasion must be treated after the pain evaluation on mucosa

The patients will be asked to assess the pain on a 10 cm visual analogue scale (VAS) with the endpoints 'no pain' and 'severe pain'. The pain from cautery will also be assessed by a verbal rating scale as "none, "slight", "moderate" or "severe" where
Slight pain = quite tolerable
Moderate = not quite tolerable
Severe = intolerable

The patients will be asked about any feeling of discomfort during the application. Local reactions such as redness, paleness or edema will be assessed according to a rating scale as none, mild, moderate or profound.

Section 7.2.2.2Statistical Analysis:

Efficacy in the pilot study was the pain score measured on a 100 mm VAS to a forceps pinch after application on EMLA in a 10-20 minute interval after application to determine anesthetic onset time.

In the main study the efficacy variables were pain scores recorded on the 100 mm VAS recorded at 10, 15, or 20 minutes (when the surgical procedure was begun) after application of EMLA, VRS scores, and the need for supplementary anesthesia.

In an earlier trial the proportion of patients not needing supplementary analgesia during cautery of condylomas on the genital mucosa was 0.4 with application times exceeding 30 minutes. Assuming that with an optimal application time in part I this proportion is 0.8, 40 patients allows detection of an improvement in need for supplementary analgesia compared to the earlier trial with a power of 95% at a significance level of 5%.[Vol. 44.4, pp. 32-34.]

Section 7.2.2.3Protocol Amendments:

Amendment 1 was dated June 12, 1986.It provided that additional anesthesia may be given by infiltration anesthesia or EMLA cream. If EMLA cream is used dose, application time and analgesic effect for this treatment should be recorded as comments on the case report form. This modification was agreed upon before any patient has been included into the trial. [Vol. 44.4, p 39.]

Section 7.2.2.4Conduct of the Study:

According to the sponsor, the treatment groups were matched in terms of demographic parameters. See Reviewer's Table 15 below:

	Pilot Study (n=10)	10 min (n=13)	15 min (n=19)	20 min (n=10)
Age (median, range)	22 (18-25)	22 (18-25)	22 (18-26)	20.5 (18-28)
No. of warts/clusters (median, range)	4 (2-10)	3 (1-15)	5 (1-10)	3 (2-11)
Location of warts (No. of patients)				
Introitus	10	11	14	10
Vestibule	-	10	16	7
Labia minora	1	5	6	1

The patients' age, the number of warts/clusters treated, and the location of the treated area. [Vol. 44.4, p. 18.]

Reviewer's Table 15A. PATIENT DISPOSITION

Treatment Groups, Application Times	Patients Enrolled	Patients Exposed	Patients Evaluable
Pilot Study 5-10 minutes	10	10	10
Main Study: 10 minutes	13	13	12
15 minutes	19	19	18
20 minutes	10	10	10

Two patients were excluded. One woman in the ten minute group was excluded from the efficacy analysis (Pat. No. 107). The investigator cauterized a few warts in this patient, but decided to interrupt the treatment as the patient was very nervous and distressed (She had earlier been scared during cautery.) No pain assessment was made. One patient who was to be treated for 15 minutes had the cream applied for only 13 minutes (Pat. No. 124). She was excluded from the analysis of the time-response of both local reactions and efficacy. [Vol. 44.4, p.10.]

Section 7.2.2.5 Sponsor's Efficacy Results:

Concomitant medication

Six patients were receiving other medication than oral contraceptives at the time of entry into the study.

Pat. No.	Application time (min)	Medication
8	10	Insulin
102	15	Cefadroxil
104	15	Pyridostigmine
105	10	Insulin
115	10	Thyroxine
		Multivitamin preparation
135	20	Phenytoin

Concomitant medication at the time of entry into the study (oral contraceptives not included). Reviewer's Table 16. [Vol. 44.4, p. 18.]

Time of onset of anesthesia (Pilot study)

The pain ratings of the forceps pinch before EMLA was given ranged from 26 to 76 (median 53.5) on the VAS. After five minutes application of EMLA the pain was rated between 0 and 12 (median 7). All ten patients were completely anesthetized within seven minutes (median 6 minutes.)

Analgesic efficacy

The investigator interrupted the cautery when the patient indicated "moderate pain". The rating "severe pain" was thus not used.

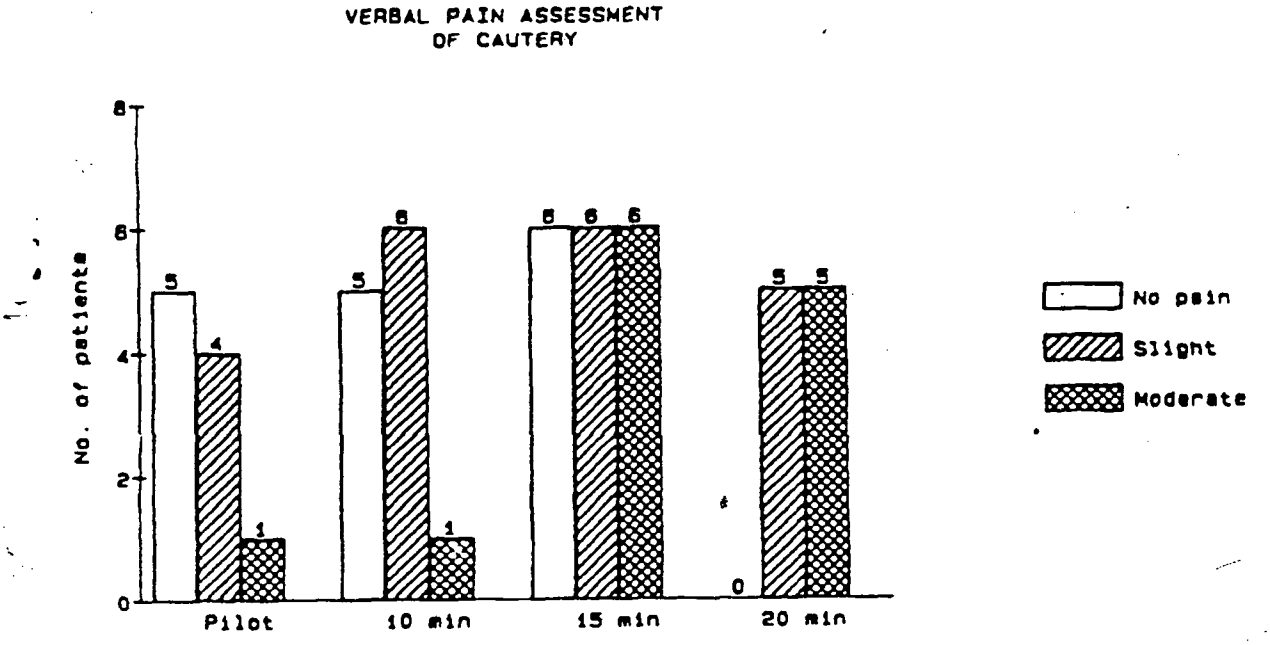
In the pilot study the cautery was performed immediately after the patient was anaesthetized, as measured by the pinch, or after a further 3-4 minutes (two patients). Application times before the cautery were between 5 and 10 minutes (median 6.5 minutes). Nine out of ten patients rated the pain from the cautery as either none or slight. The VAS scores ranged from 0 to 56 (median 0).

[Vol. 44.4, pp.10-11.]

The verbal pain assessments indicated a significant increase in pain with increasing application time. The median VAS scores increased from 7 to 34.5 with increasing application time, but the trend did not reach statistical significance.

	VAS 10 min	VAS 15 min	VAS 20 min
Median	**7.0**	29.0	**34.4**
Mean	18.7	31.3	35.7
Minimum	0	0	7
Maximum	53	67	72
Number of Obs.	12	18	10

Reviewer's Table 16A. [Vol. 44.4, p.21.]



Verbal pain ratings (main study; $p < 0.05$). The patient who has EMLA applied for 13 minutes felt slight pain (not included in the figure).Main study, $p<0.05$, Mantel-Haenszel test) Reviewer's Figure 4. [Vol. 44.4, p.12.]

Total doses given

The total doses of EMLA given on the genital mucosa in patients receiving additional analgesia ranged from 7.5 - 12.5 g (median 7.75 g). Five women received a further 2.5-5 g (median 5 g) on the perigenital skin.

Pain from injection of additional anesthetics

The pain from the additional injection of local anesthetics after pretreatment of the mucosa with EMLA was assessed as slight in 4/6 women and at 16 to 64 (median 33.5) on the VAS.

Adverse reactions

No sign of systemic reactions was seen in any of the patients.

Section 7.2.2.6Reviewer's Efficacy Discussion

The results of this study indicate that EMLA showed efficacy, in 5-10 minutes ($p<0.05$), in producing adequate anesthesia for the cautery of condylomata acuminata in most patients studied. There were no reports of systemic AEs but there were reports of mild local reactions. Unfortunately this study does not use any control (either placebo or active) to judge the comparative efficacy or safety of this drug. Therefore, in the opinion of this reviewer, this trial, while supportive, is not adequate or well controlled and does not provide sufficient evidence to be considered "pivotal".

SECTION 7.2.3 STUDY 83P026:2

Section 7.2.3.1Protocol Synopsis:

Title: A Double Blind, Randomized Comparison Of A 2% And 5% Lidocaine-Prilocaine Cream (EMLA) As Anesthesia For Cervical Curettage

Objectives:

To compare the analgesic effect of EMLA 2% and 5% cream used for cervical curettage
To evaluate if any of the creams, applied only in the fornices, provides adequate analgesia for cervical curettage.
To evaluate possible adverse reactions.
To subjectively evaluate the overall clinical usefulness.
To evaluate the attitude of the patients towards EMLA as an analgesic for this procedure. [Vol. 44.4, p.98.]

Study Design: The study is a double-blind trial of parallel group design. Each patient entering the study will be assigned at random with equal probabilities to either Group I or Group II (see below):
Group I: EMLA 5% cream, 2 x 5 ml
Group II: EMLA 2% cream, 2 x 5 ml.

Before entering the study the patients were to be informed about the trial and the procedures involved and a written information was also to be given to the patient. An oral consent to participate was to be obtained.

After colposcopy was to have been carried out 2 x 5 gram of the cream is applied in the lateral fornices and a cotton swab moistened with saline is applied to keep the cream in the fornices. The application time was to have been 10 minutes. Toward the end of the application time the patient was to be asked for any discomfort caused by the cream. The cream was to be then washed away with saline soaked cotton swabs and portio and vagina are observed for any local adverse reactions. After cleaning with 0.5% chlorhexidine solution the cervical curettage was to be carried out and the patient asked to assess the pain. Before discharge the patient was to be asked about her attitude towards EMLA in case of a repeated procedure.

Evaluation of analgesic effect

The patient will be asked to evaluate pain from the procedure in accordance

with a four graded verbal rating scale:

- no pain
- slight pain. Slight feeling of discomfort but quite acceptable
- moderate pain. Pain is clearly evident but the procedure can be carried out without any additional analgesia
- severe pain. Pain necessitating supplementary analgesia or if the procedure is already finished, a judgement that it should not have been carried out if the poor effect had been anticipated.

The women will be asked about any problems such as itching, smarting pain or other after the application of the cream. Vagina and portio will be inspected for any local adverse reactions such as redness, paleness, edema and other changes. The overall clinical judgement including factors such as practical usefulness of the procedure, application procedure, application time, analgesic efficacy, and adverse reactions will be registered according to a four-graded scale. The patient will be asked if EMLA would be accepted as analgesic method in case a future cervical curettage has to be performed or if she thinks she would prefer a PCB or general anesthesia. [Vol. 44.4, pp.100-102.]

Section 7.2.3.2Statistical Analysis:

Parameters to be assessed included patient's uneasiness before the operation (measured on a 100mm VAS), analgesic effect (measured on a 4 point VRS). Nonparametric statistical methods will be used to test hypotheses about parameters in Group I and Group II. Descriptive statistics and graphical displays will be used to characterize the patient material. All patients included in the trial will be evaluated with respect to safety. [Vol. 44.4, p.104.]

Section 7.2.3.3Protocol Amendments:

Amendment 1 date not given, states that because the first 10 patients in the pilot study did not produce convincing evidence for the most efficacious application time, the pilot study was extended and the pharmaceutical properties of pH and viscosity were considered as possible influences. When the study

was concluded, 39 patients had been treated. The main part of the study comparing 2% and 5% creams was postponed and a new study comparing EMLA with PCB will be initiated. [Vol. 44.4, p.106.]

Section 7.2.3.4 Conduct of Study:

The primary efficacy endpoint is the analgesic effect as measured by the pain score recorded on the 100 mm VAS. Secondary efficacy endpoints include pts uneasiness, level of discomfort, pts. acceptance of EMLA in the future, and overall clinical acceptance.
As discussed in the protocol above, the sponsor instituted a new study under this study number (83-P026) with the title, "An Open Label Study On 5% Lidocaine-Prilocaine Cream, EMLA, Used As A Topical Anesthetic For Cervical Curettage". This was a non randomized, single dose study involving 39 women between 18-47 years These women were scheduled for cervical curettage due to cervical intraepithelial neoplasia. The dosage regimen was 10 mL 5% EMLA cream with pH 8.5 or 9.5 applied to the lateral fornices (5mL on each side). Pre-medication (diazepam) was given to 3 patients. No other current treatment was given.

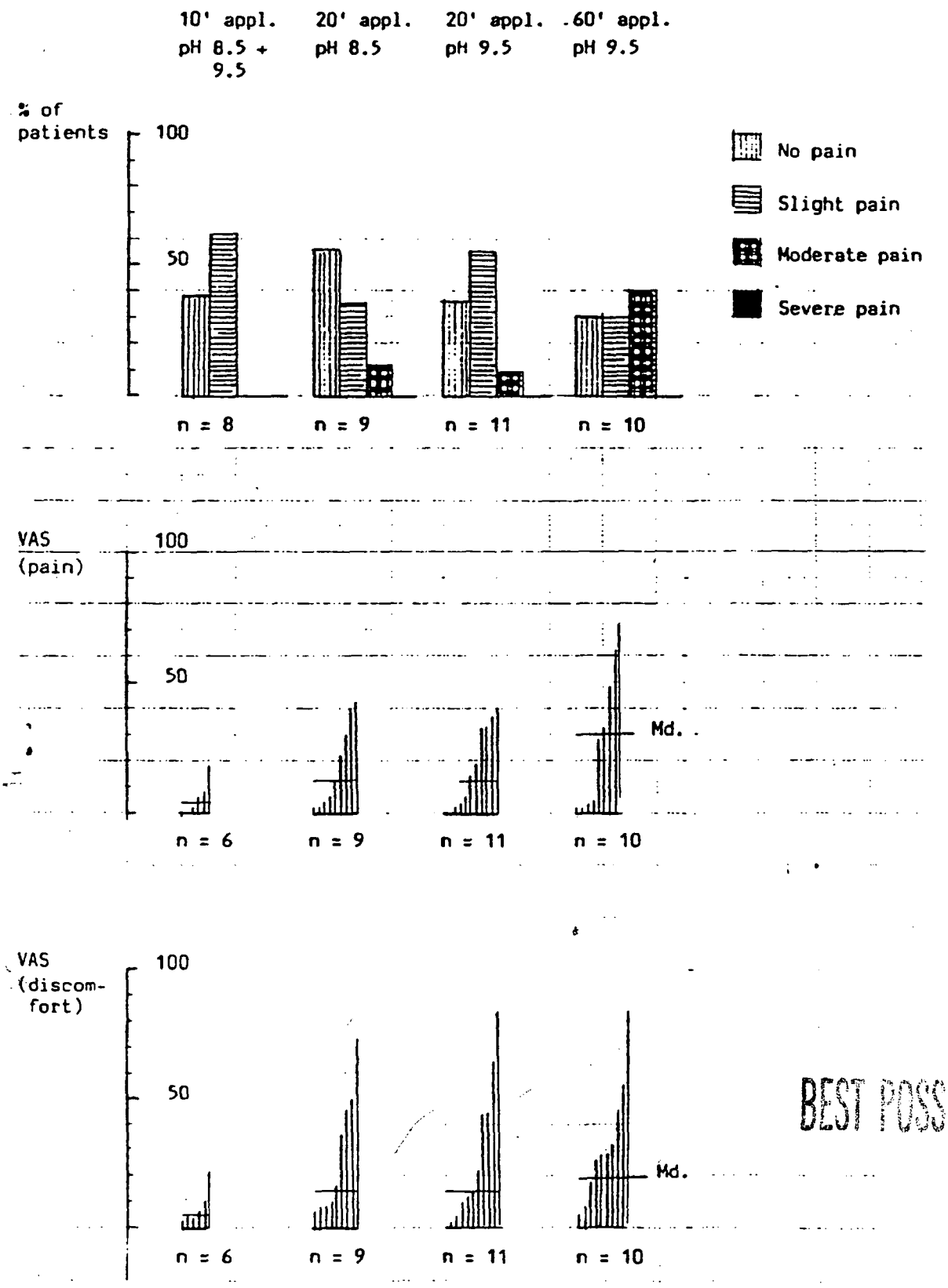
Investigational Methods: 1. The patient assessed the degree of her uneasiness before the start. of the operating procedure on a visual analogue scale (VAS). 2. After colposcopy the cream was applied. The application time was 10, 20 or 60 minutes. In the patients with 60 minutes application, colposcopy was carried out after removal of the cream. 3 The patent was asked about any discomfort caused by the cream and portio and vagina were inspected for any local adverse reactions, 4. Venous plasma levels were drawn 30, 60, and 90 minutes after the start of application in the group, which had 60 minutes' application time. 5. Cervical curettage was carried out and the patient assessed her degree of pain and discomfort on a 4-point verbal scale and on a VAS. 6. At a final interview the patient was asked if she would consider EMLA anesthesia in the event of a repeated curettage. 7. The investigator made an overall subjective evaluation of the usefulness of the cream. [Vol. 44.4, p.72.]

Reviewer's Table 16B.PATIENT DISPOSITION

Application Times	Patients Enrolled	Patients Exposed	Patients Evaluable
10 minutes	8	8	8
20 minutes	21	21	21
60 minutes	10	10	10

Section 7.2.3.5Sponsor's Efficacy Results

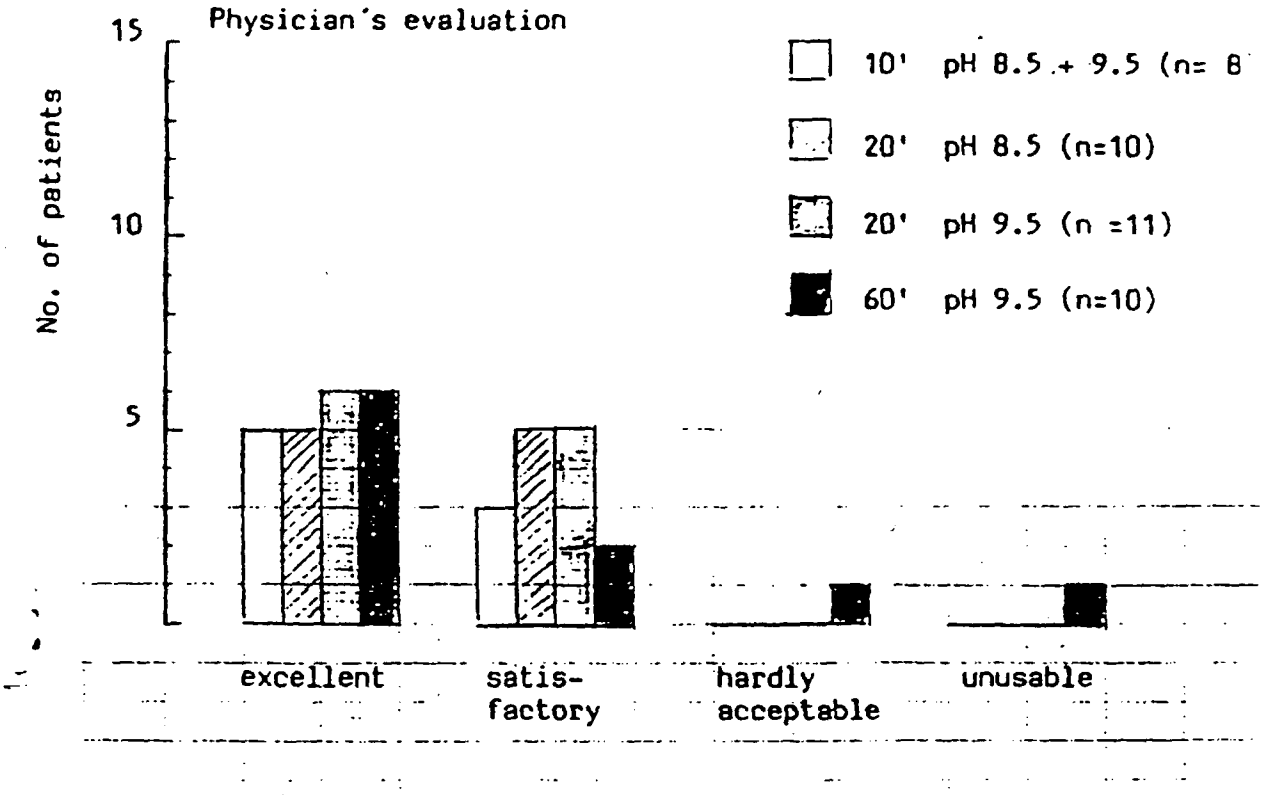
Patient's uneasiness before the operation (measured on a 100mm VAS) ranged from 0 to 99 with a median of 37. Analgesic effect including both pain and discomfort were to be measured on a 100mm VAS and a 4 point VRS. A 10 minute application had a median pain score on VAS of 5 mm, a 20 minute application had a median pain score on VAS of 15 mm, and a 60 minute application had a median pain score on VAS of 20 mm. There was a significant correlation between application time and VAS pain scores (P=0.038). [Vol. 44.9, p.36.]



Reviewer's Figure 5 Assessment of pain and discomfort within the different groups. [Vol. 44.4, p.90.]

5. All procedures were assessed as "excellent" or "satisfactory" with 10 or 20 minute application times. With 60 minute application time one was found to be barely acceptable and one unusable.

Reviewer's Figure 6

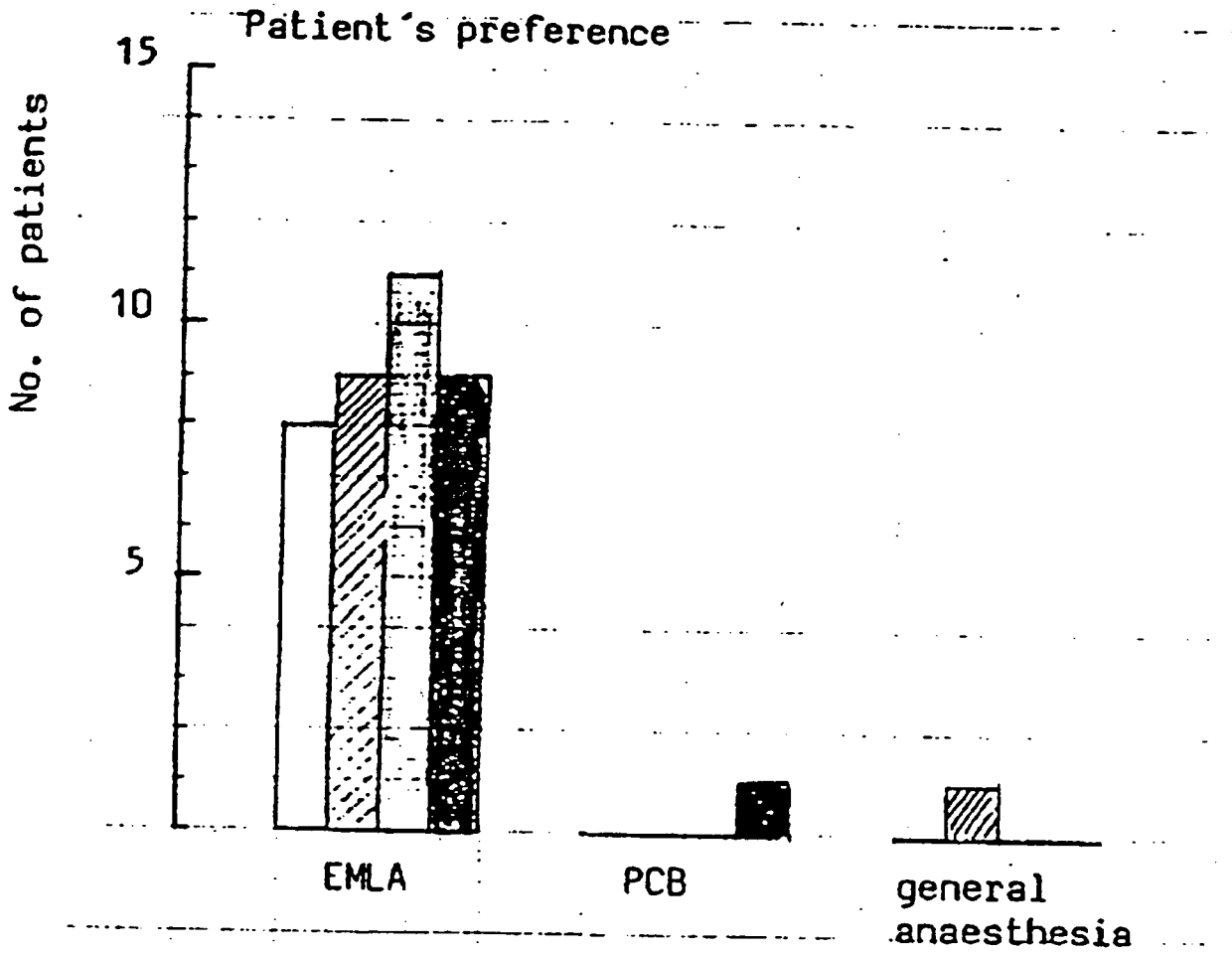


[Vol. 44.4, p.92.]

6. All eight patients with 10 minute application times, 20 out of 21 with 20 minute application times, and 9 out of 10 patients with 60 minute, application times would prefer EMLA in the event of a future cervical curettage.

[Vol. 44.4, p.92.]

Reviewer's Figure 7.



[Vol. 44.4, p.72.]

7. Plasma samples were obtainable from 9/10 patients, since there were sampling problems with one patient.[Vol. 44.4, p.83.] Highest individual peak concentration was 641 ng/mL for lidocaine and 286 ng/mL for prilocaine

8. Variation in pH of the cream (8.5 or 9.5)did not affect the analgesic efficacy or the incidence of local reactions. [Vol. 44.4, p.84-85.]

Section 7.2.3.6Reviewer's Efficacy Discussion:

Unfortunately this study, like the previous one (86EM04 Part 1), was an open label trial without randomization, blinding, or use of any control (either placebo or active) to judge the comparative efficacy or safety of this drug. Therefore, in the opinion of this reviewer, this trial, while it provides information, is not adequate or well controlled and does not provide sufficient evidence to be considered "pivotal".

SECTION 7.2.4 *STUDY 90EM 11*

Section 7.2.4.1 Protocol Synopsis:

Title: A Double Blind Study On The Topical Analgesia Experienced With EMLA Cream As A Premedication To Infiltration Anesthesia In The Genital Mucosa Of Women

Objectives: The aim of the study to evaluate the efficacy of EMLA cream in obtaining topical analgesia before local infiltration into the external vulva of the genital mucosa of women.

Study design: This Phase III trial is a randomized, double blind, placebo controlled, parallel group study of 44 female patients, 18 years or older, who are scheduled for biopsy or a surgical procedure of the external vulva of the genital mucosa. After informed written consent is obtained, the patient will be enrolled in the study and assigned the first available study number as dictated by the randomization list. The study tube with the corresponding study number will be selected and the patient will have 2 - 5 grams of EMLA/placebo cream applied in a thick layer on the site selected for infiltration on the external vulva of the genital mucosa. If the cream is not completely covered naturally, a plastic dressing may be applied. The cream will be left in place for at least five minutes and not greater than ten minutes. During the application, the patient will be questioned about any local sensations they might be experiencing. The cream will then be wiped off and the investigator will observe and record any local reactions. The local anaesthetic injection will follow immediately after removal of the cream. Local infiltration will be performed with a Becton Dickinson 25 Gauge needle and Xylocaine 1% with adrenaline. It will be injected at a rate of 1 ml/5 seconds as counted by the investigator. The volume of infiltration will not be less than 1.0 ml and will be recorded in all cases. The type of surgery performed will be

recorded. Each patient will receive only one application of either EMLA Cream or EMLA Placebo during the course of the study. [Vol.44.3, pp.223-224.]

Immediately following the infiltration of local anaesthetic and prior to the biopsy, the patient will be asked to assess the degree of pain and discomfort associated with the injection on a Visual Analogue Scale (VAS).The degree of pain and discomfort associated with the injection of the local anaesthetic agent will be assessed by the patient before the surgical procedure is started, on a 100 mm Visual Analogue Scale (VAS) with the endpoints "No pain" and "Intolerable pain". The patients will mark an X on the scale. After the VAS has been marked, the pain will also be assessed by the patient on a verbal rating scale as None, Slight, Moderate or Severe where:
None = no pain
Slight pain = quite tolerable
Moderate pain = not quite tolerable
Severe pain = intolerable
The use of the VAS will be explained to the patient by a comprehension test prior to inclusion into the study. There will be no laboratory assessments made during this study. During the application period, the investigator will ask the patient about the presence of a burning or itching sensation, or any other local sensations they might be experiencing. Immediately after removal of the cream, the investigator will assess the area for any redness, or edema according to a four-point Verbal Rating Scale (VRS) as: None, Mild, Moderate or Severe. Any other adverse events shall be marked and specified on the patient record forms. [Vol. 44.3, pp. 225-226]

Section 7.2.4.2 Statistical Analysis

A VAS and a VRS score will be the efficacy variables.

T-test and Fisher's exact tests were used to test the baseline characteristics between the EMLA and placebo treatment groups. Differences in the main efficacy parameter, VAS pain scores, following EMLA and placebo were evaluated by nonparametric methods: Wilcoxon rank sum test. In this study the two-sided alternative was considered and a P-value of $< 0.0\sim$ was regarded to be statistically significant. Average pain scores were calculated for each treatment. Patients

were excluded from the statistical analysis of analgesic efficacy if:

- an inclusion/exclusion criterion was violated.
- cream application was less than 5 minutes or greater than 10 minutes.
- more than 10 minutes elapsed between the removal of the cream and the start of the infiltration.

No interim analysis was performed for this study. [Vol. 44.3, p.191.]

Non-parametric methods will be used to test the difference in pain between the EMLA and the placebo treated groups.

Patients will be excluded from the statistical analysis of analgesic efficacy if:

a. the application time of the cream is less than 5 minutes:
b. the application time of the cream is more than 10 minutes;
c. more than 10 minutes elapsed between the removal of the cream and the injection.

Twenty-two patients in each group will allow detection of a difference in visual analogue pain score of 20 mm between the groups with a power of 90% at a significance level of 5% (s.d. = 20 mm). [Vol. 44.3, pp.231-232.].

Section 7.2.4.3Protocol Amendments

None

Section 7.2.4.4Conduct of the Study

The study was performed as per the protocol with the following changes:

1. It was planned that patients would be stratified, for biopsy or other surgical procedure, to ensure that an equal proportion of patients were scheduled for biopsy in each treatment group However this was not necessary as all patients had a biopsy in this study.[Vol. 44.3, p.183.
2. A thick layer (2-4 g) of EMLA or placebo cream was used but the protocol called for up to 5 g.

Reviewer's Table 16C. PATIENT DISPOSITION

Treatment Groups, Application times	Patients Enrolled	Patients Exposed	Patients Evaluable
EMLA Cream, 6-10 minutes	22	21	21
Placebo,6-9 minutes	23	23	23

One patient (patient #121) was excluded from the trial prior to receiving any treatment but after randomization into the study. This patient took an analgesic pain relieving medication (ASA) in the four hours prior to treatment violating the inclusion/exclusion criteria. This patient was not evaluated at all. [Vol. 44.3, p.194.]

Section 7.2.4.5Sponsor's Efficacy Results:

The patient's VAS scores indicated that significantly less pain (p-value <0.005) was experienced with EMLA (mean = 23.38 mm) compared to placebo (mean = 43.00 mm). From the patient's VRS Scores; 52.2% in the placebo group but only 23.8% in the EMLA group experienced moderate or severe pain. Three patients in the placebo group and no patients in the EMLA group experienced severe pain. [Vol. 44.3, p.181.]

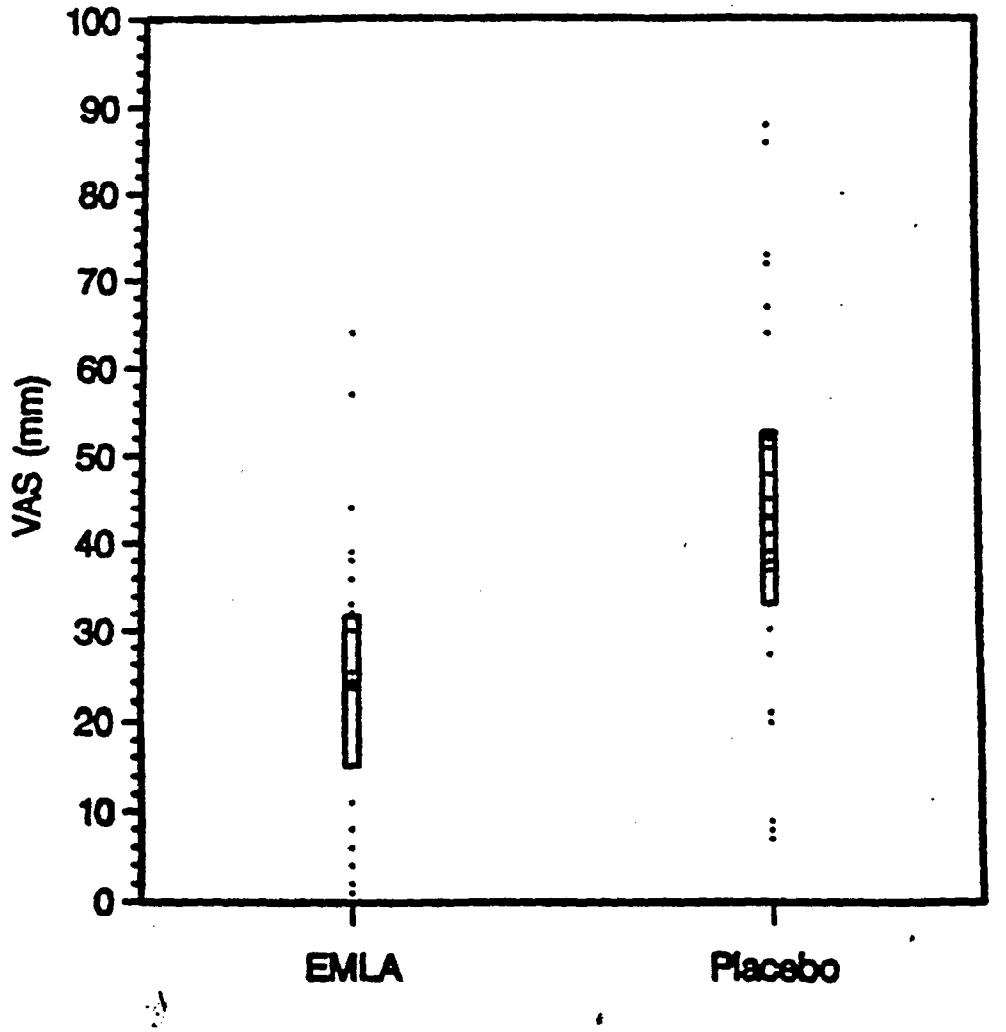
Reviewer's Table 16. Descriptive statistics of VAS pain scores (mm), evaluated by the patient, by treatment (N=44)

		Treatment	
		EMLA	Placebo
TOTAL	Number	21	23
VAS SCORE (mm)	Mean	23.38	43.00
	Std. Dev.	18.99	23.55
	Range	1.00 - 64.00	7.00 - 88.00

[Vol. 44.3, p. 206.]

Pain Evaluation – Visual Analogue Scale (mm)

Plot of VAS scores with Mean ±2 STD(mean). EMLA: N=21, Placebo: N=23.

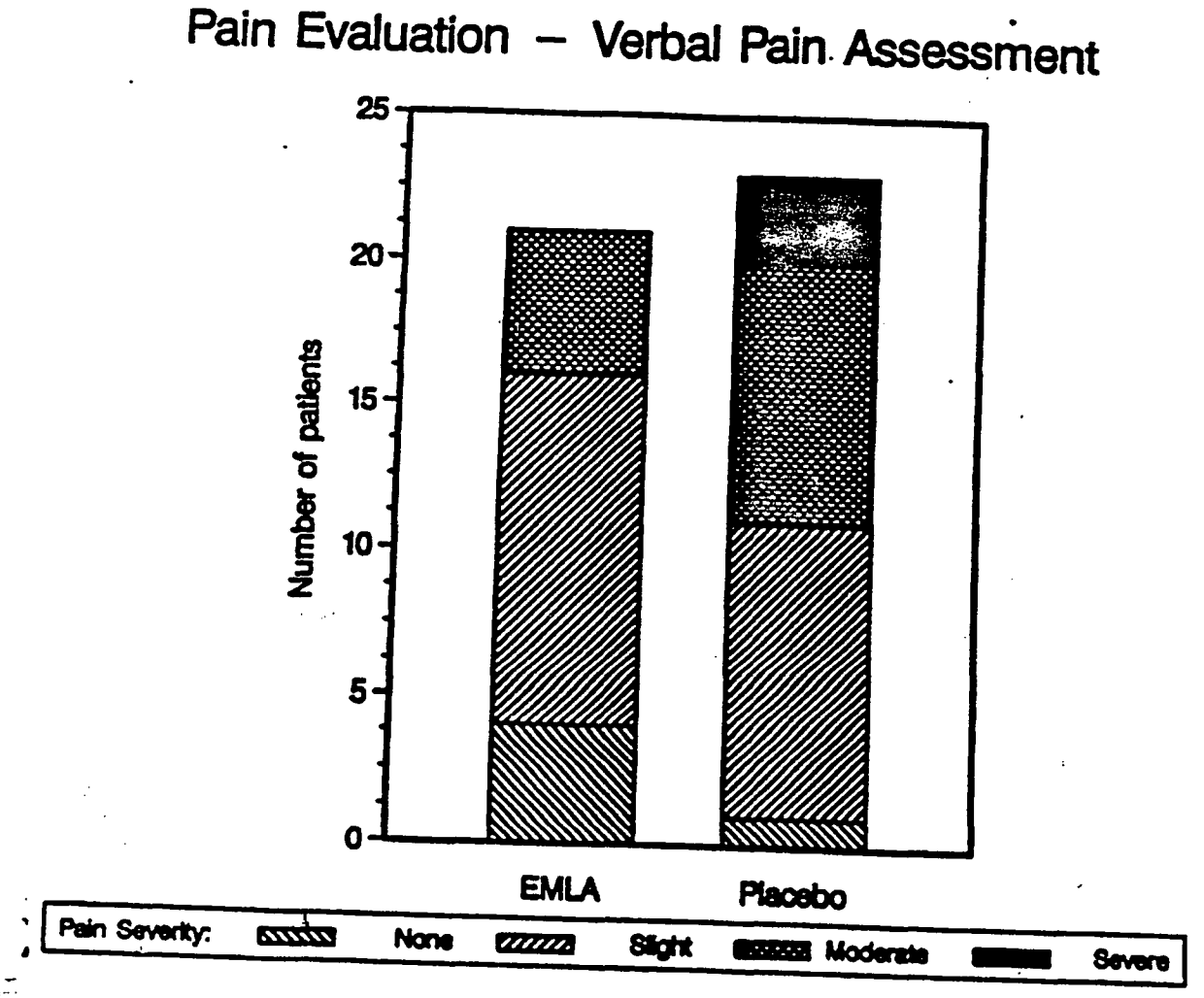


Reviewer's Figure 8.[Vol. 44.3, p.212.]

Reviewer's Table 17. Descriptive statistics of VRS pain scores, evaluated by the patient, by treatment (N=44)

		Treatment	
		EMLA	Placebo
TOTAL	Number	21	23
VRS PAIN SCORE	None	4	1
	Slight	12	10
	Moderate	5	9
	Severe	0	3

[Vol. 44.3, p.206.]



Reviewer's Figure 9. [Vol. 44.3, p.213.]

Section 7.2.4.6Reviewer's Efficacy Discussion:

The results from this study indicate that EMLA provided a statistically significant reduction in pain on infiltration injection to the genital mucosa of women. When applied 6-10 minutes before injection, the VAS scores for the EMLA group were significantly lower (<0.005) than the placebo group. The VRS scores also showed a marked difference in pain scores favoring the EMLA group over the placebo group.

Section 7.2.5 Other Supporting Clinical Trials

84EM12 A randomized, double blind, placebo-controlled, parallel group, single center study comparing EMLA (10 mL) to placebo (10mL) as a topical anesthetic for insertion of an IUD. Comparing EMLA applied 11-21 minutes to placebo 11-19 minutes. 44 females patients (23 on EMLA). EFFICACY RESULTS: The mean pain score from insertion of the IUD was 20 mm in the EMLA group and 15 mm in the placebo group (no significant difference). 39% in the EMLA group and 48% in the placebo group had an IUD removed before insertion of the new one. The mean VAS pain score on removal was 32 mm in the EMLA group and 29 mm in the placebo group (no significant difference). EMLA CREAM APPLIED TO THE FORNICES FOR 11 TO 21 MINUTES WAS NO BETTER IN REDUCING PAIN FROM IUD INSERTION THAN PLACEBO. SAFETY RESULTS: Local reactions seen were vaginal redness burning sensation, tingling, or feeling of warmth and all were mild and transient. [Vol. 44,6, p.142.]

End Points:

I.. Evaluation of analgesic effect. Evaluation to be done on a VAS from "not painful" to "very painful".

II. Evaluation of attitude toward the cream

III. Evaluation of overall clinical assessment from excellent, satisfactory, only just acceptable, to unacceptable.

83PO36. An open label, single center study of EMLA used as topical anesthetic for pain prevention during vacuum abortion. Comparing EMLA applied 10 minutes in fornices plus paracervical injections of 0.9 % saline, EMLA 10-20 minutes in fornices, and EMLA in fornices and cervical canal for 20 minutes. 20 female patients. EFFICACY RESULTS: The highest peak venous plasma concentration s were 549 ng/mL for lidocaine and 346 ng/mL for prilocaine, which are well within safe margins. IN MOST CASES THE ANALGESIC EFFECT WAS INADEQUATE FOR DILATATION OF THE CERVICAL CANAL. 13 out of 20 patients needed general anesthesia before the operation could be carried out.

SAFETY REULTS: Slight paleness in the vaginal mucosa was seen in two patients but not other local reactions were observed. . [Vol. 44.6, pp. 197, 209.]

End Points:

I. Evaluation of analgesic effect

II. Subjective evaluation of the application.

III. Evaluation of local adverse reactions.

IV. Overall clinical judgement

81PO29 An open label, uncontrolled, single center study of EMLA 2% used as an anesthetic agent for cervical curettage and vacuum abortions in the fornices 6-25 minutes for cervical curettage and 10-60 minutes in the abortion group. 31 female patients. EFFICACY RESULTS: Maximum peak plasma concentrations of lidocaine and prilocaine were 156 and 48 ng/mL respectively. In the curettage group 19 patients reported no pain, 7 moderate pain, and one patient severe pain. In the abortion group one reported no pain, one moderate pain, and two severe pain, both necessitating supplementary anesthesia. The investigators felt EMLA was acceptable as an alternative to routine anesthesia for cervical curettage but was unsatisfactory in the abortion group though v the number of patients was too small to draw any conclusions. SAFETY RESULTS: Investigators felt local irritation was insignificant. There was no indication of cellular changes due to EMLA in the histopathological examinations. [Vol. 44.6. pp.268, 273.]

End Points:

I. Local discomfort caused by cream application.

II. Analgesic effect i.e. pain score during the operation.

LIST OF POSSIBLE ALTERNATIVE PIVOTAL STUDIES

Study 84EM07 is a randomized, double blind, placebo-controlled, parallel group, single center, study of the effects of EMLA as a topical anesthetic for cervical curettage. 60 female patients in the study of which 30 received EMLA(10 mL), and 30 patients received placebo cream(10mL). EFFICACY RESULTS: The mean pain score was 21 mm in the EMLA group and 28 mm in the placebo group (not significant). The mean discomfort score was

24 mm in the EMLA group and 38 mm in the placebo group ($p<0.05$). The investigators felt that local application of EMLA in the vagina significantly reduces discomfort but did not produce sufficient analgesic effect during portio biopsy and cervical curettage. SAFETY RESULTS: The majority of patients showed no local reactions and in no case did the local reaction require treatment. [Vol. 44.3, p. 97.] Note: Although this trial is considered by the sponsor to be supportive, it is an adequate and well-controlled trial. Unfortunately, it does not show efficacy. Dr Sue Jane Wang has included this study, along with Study 86EM07, in her efficacy analysis for the indication of topical minor surgery.

End Points:

I.. Analgesic effect measured on a 100 mm VAS by patient.

II. Patient preference for same type of treatment in the future

I. Overall clinical assessment by physician on 4 point scale judging ease of procedure, analgesic efficacy, and AEs. Scale included ratings of excellent, satisfactory, only just acceptable, unacceptable.

II. Local reactions assessed by asking patient about burning, itching or other local irritation and physician's evaluation of redness, pallor or edema. Any other AEs.

Study 86EM12 is open-label, randomized, comparative, parallel group, multi-center study of the anesthetic effect of EMLA during diathermy treatment of condylomata acuminata. One group had EMLA cream applied for 60 minutes, one group EMLA Cream applied 10 ml for 5C minutes with an additional 5 ml of EMLA applied at 50 minutes (top-up), and one group had infiltration as supplementary anesthesia if needed (mepivacaine/epinephrine which was originally supposed to be 10mg/ml of prilocaine). 32 female patients of which 19 received EMLA for 60 minutes and 20 received a top-up dose of EMLA at 50 minutes (for an additional 10 minutes). EFFICACY RESULTS: The study was stopped when 42 out on an intended 60 patients had been recruited due to slow patient inclusion rate. THE INVESTIGATORS STATED THAT NO CONCLUSION WAS POSSIBLE WITH RESPECT TO EFFICACY. SAFETY RESULTS: Burning pain was felt by 18 patients. Local edema was observed in four patients, local redness in 3 patients, and local paleness in 1 patient. Four patients reported local AEs: one patient reported slight pruritis, one a slight

numbness, one a heat sensation, and one reported an "anesthetic feeling". [Vol. 44.4, p.157, 168.]

End Points:

I. Patient assessment of pain from supplementary anesthesia injection on a 100 mm VAS.

II. Patient evaluation of pain from the whole procedure (including pain from injection) on a 100 mm VAS

III. Patient's global assessment.

IV. PK assessment

V. Local AEs assessed by patient's evaluation of burning, or itching and skin was inspected for redness, pallor, or edema.

STUDIES EM9404, and 84EM11 as the only two studies in which males were studied.

Study EM9404 is an open-label, randomized, parallel group, multi-center study to compare the analgesic efficacy of EMLA to infiltration of lidocaine for biopsies of the genital mucosa. One group received EMLA cream for 7-12 minutes and the other group received 1% lidocaine injection (not more than 200 mg or 20 mL). The EMLA group consisted of 9 male and 22 female patients, and the lidocaine group consisted of 8 male and 24 female patients. <u>EFFICACY RESULTS:</u> There was a statistically significant difference in pain score in favor of lidocaine during the biopsy ($p<0.05$). EMLA showed a statistically significant difference in pain score for anesthetic technique ($p<0.05$). <u>SAFETY RESULTS:</u> Local reactions were more numerous in the EMLA group(n=19) than in the lidocaine group (n=8) ($p<0.05$). Pallor and burning were the most frequent reactions with EMLA. [Vol. 44.5, p. 36.]

End Points:

I. Patient evaluation of pain induced by the biopsy on a 10 point VAS.

II. Patient evaluation of pain caused by the lidocaine infiltration or the application of EMLA on a VAS.

III. Patient evaluation of local tolerance to EMLA injection such as burning, pain, pruritis, and redness, pallor, or edema.

Study 84EM11 is an open-label single center study on the use of EMLA as a topical anesthetic for cautery of genital warts. 10mL of Cream applied. Patients were divided into two groups. One group was only male and had EMLA applied for 20-70 minutes. The other group was female and had EMLA applied for 30-105 minutes. There were 57 male patients and 51 female patients. EFFICACY RESULTS: Investigators felt that analgesia was sufficient in 96% of men and 40% of women. Additional local infiltration was given to 60% of women but was not as painful as injections generally are in the genital area. SAFETY RESULTS: Local pallor was observed in 30 % of patients, redness in 20 %, and edema in 15%. Investigators noted no discomfort was reported and also felt these changes were not clinically significant.[Vol. 44.6, p.6.]

End Points:

I. Physician assessment of pain on a 4 point graded scale from no pain (0), slight pain (1), moderate pain (2), to severe pain (3).

II. Local AEs such as redness paleness or edema reported on a four point graded scale from no, slight, moderate, to severe.

Section 7.2.5.1 Literature Documents

The sponsor submitted 23 literature references. Of these, this reviewer felt that only 12 either provided adequate and well-controlled trials or contained information to support this submission. Those references are summarized below:

X3 Van Der Burght M, Schonemann NK, Laursen JK, Arendt-Nielsen L, Bjerring P. Duration of analgesia following application of Eutectic mixture of local anaesthetics (emla) on genital mucosa. Acta Derm Venereol 1993;73(6):456-8. This was an open label, cross-over study in healthy female volunteers Duration of anesthesia on genital mucosa was determined by argon laser experimental pain model after treatment with EMLA for 5, 10, or 20 minutes. N=12. The average duration of analgesia was between 16 and 22 minutes after application for 10 minutes with EMLA. [Vol. .44.9, pp.53-54.]

X4 Stigliano CM. Mollo A, Zullo F. Two modalities of topical anesthesia for office hysteroscopy. Int J Gynaecol Obstet 1997; 59:151-2. This was an open-label, randomized parallel group study comparing efficacy of 3 g of EMLA applied for 10 minutes to: Xylocaine® spray treatment , and to untreated controls for hysteroscopy. N=88 patients exposed to EMLA. The time to complete the examination was significantly reduced in the EMLA group compared to both the Xylocaine and control groups. P<0.05. [Vol. 445.9, pp.55-56.]

X5 Miller I., Jensen MP, Stenchever MA. A double blind randomized comparison of lidocaine and saline for cervical anesthesia. Obstet Gynecol 1996:87(4):600-4. Fifty-two of 135 eligible women participated. The authors concluded that to minimize lidocaine toxicity, bacteriostatic saline or very dilute lidocaine could be considered for paracervical injection.

X6 Lipscomb GH, McCord ML, Bain KW, Ling FW. The effect of topical 20% benzocaine on pain during loop electrosurgical excision of the cervix. Am J Obstet Gynecol 1995; 173(3):772-4. This was a double blind, placebo controlled, randomized study. 50 women received 20% benzocaine or placebo gel. Pain to cervical injection and tissue excision was measured on a VAS. The authors concluded that 20% benzocaine does not appear to reduce he pain of injection of tissue excision.

X7 Rylander E. Sjoberg I. Lillieborg S, Stockman O. Local anesthesia of the genital mucosa with a lidocaine/prilocaine cream (EMLA) for laser treatment of condylomata acuminata: A placebo controlled study. Obstet Gynecol 1990; 75:302-6. 80 women were randomly allocated to EMLA or placebo 1-75 minutes before CO_2 laser treatment. Most effective anesthesia was 5-15 minutes after EMLA application. All EMLA patients had significantly less pain than placebo.

X8 Rabin JM, Spitzer M. Dwyer AT, Kaiser IH. Topical anesthesia for gynecologic procedures. Obstet Gynecol 1989,73(6): 1040-4. This was a placebo

controlled randomized study. In phase 1, 82 women received one or more of the following procedures: cervical biopsy, IUD insertion, endocervical curettage, paracervical block, and tenaculum placement. Study drug patients reported significantly less pain than placebo (P<.05 to P<.0005). In phase 2, 127 women in a blinded fashion underwent the same procedures as in phase 1. The authors concluded that 20% benzocaine significantly reduces pain after many gynecologic procedures performed vaginally.

X9 Clifton PA, Shaughnessy AF. Andrews S. Ineffectiveness of topical benzocaine spray during colposcopy J Fam Pract. 1998; 46(3):242-6. This was a double-blind, placebo controlled trial in 36 patients. No difference between active drug and placebo. Authors concluded that benzocaine spray offers no benefit for reduction of pain or anxiety in women undergoing colposcopic procedures.

X13 Wohl H. The Cusum plot: Its utility in the analysis of clinical data. N Engl J Med 1977;296(18):1044-5. Determining trends can be difficult because data has a natural degree of scatter that can obscure early detection of a trend. To use a cusum plot a reference value must be selected (ex. the approximate mean of the initial data points or a commonly used reference point). This reference value is subtracted from each data point in succession and the difference is added algebraically to the previous sum (cumulative sums or cusums).Change in slope is important but distance from the reference value is not. Change in slope represents a change in mean value. Cusum plots permit early detection of changing means and may permit short-term prediction.

X14 Maddi R, Horrow JC, Mark JB, Concepcion M, Murray E. Evaluation of a new cutaneous topical anesthesia preparation. Reg Anesth 1990; 15(3): 109- 12. This was a double blind, placebo controlled, randomized study of EMLA vs. placebo in 75 patients when applied to the dorsum of both hands prior to IV cannulation. The EMLA site was preferred ($p<0.01$). The authors conclude EMLA is effective for cutaneous anesthesia when applied under an occlusive

bandage for 45 minutes.

X15 Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lignocaine. Br J .Anaesth 1976;48:1171-4. This was a double blind trail in 31 volunteers comparing various concentrations of bupivacaine and lignocaine. Statistically significant results (P<0.001) showed constriction was observed more frequently at lower concentrations and vasodilation at higher concentrations. Duration of action was unaffected except for a longer duration for 0.5% bupivacaine.

X19 Frega A, Di Renzi F, Palazzetti PL., Pace S, Figliolinli M, Stentella P. Vulvar and penile HPV lesions: laser surgery and topic anaesthesia Clin Exp Obstet Gynecol 1993;20(2);76-81. This active control study comparing EMLA to 1-2 ml 2% carbocaine infiltration was performed on 180 men and women in the EMLA group and 90 men and women in the control group. Pain from application of anesthetic under surgery was significantly less (P<0.001) in the EMLA group.

X21 Sarkar PK, Williams Sfl, Davies-Humphreys J. A double-blind placebo-controlled trial of EMLA cream for the relief of pain associated with laser vapourisation for cervical pre-maliginant conditions. J Obstet Gynaecol 1993;13, 370-2. In this study of 70 women, the most intense pain reported by the EMLA group was less (P<0.05) than the placebo group, but there was no difference in analgesic effect using a VAS.

[Vol. 1.1, pp. ix-xi.]

SECTION 8.0 SAFETY FINDINGS

SECTION 8.1 .....METHODS:

The review of the safety of EMLA is centered on the information provided by the sponsor in their Integrated Summary of Safety (ISS) that includes all adverse events that occurred during the 14 EMLA Cream studies in patients treated on genital mucous membranes. These 14 studies were conducted between 1981 and 1984.

The repeated-dose study (89LI02 that was for relief of symptoms from Recurrent Genital Herpes applied 3x/day for three days) and the EMLA Cream 2% study are not included in the integrated analyses but were tabulated separately. Therefore, 12 studies instead of 14 are included in most data tables in the sponsor's ISS. By the definition of "Repeated-dose application" as "treatment over more than one day", Study (86EM12), which included a "top-up" dose after 50 minutes, does not qualify as a repeated-dose study. In addition, only female patients who were exposed to study drug on the mucosa or mucosa and skin were included in the sponsor's analysis. None of the male patients and those female patients exposed to drug on the skin only were included. [Vol. 44.9, p.104-105.]

SECTION 8.2 ..... SERIOUS ADVERSE EVENTS:

Section 8.2.1 Deaths:

There were no deaths reported during these clinical trials. [Vol.44.9, p.143.]

Section 8.2.2. Non-Fatal Serious Adverse Events:

There were no serious adverse events reported during these clinical trials. [Vol. 44.9, p.143.]

SECTION 8.3 ..... Assessment of Dropouts

There were no discontinuations due to adverse events during these studies. [Vol. 44.9, p.143.]

SECTION 8.4 ..... Other Significant Adverse Events

There were no other significant adverse events in the 378 female and 7 male patients exposed to EMLA Cream on mucous membranes during the studies included in the sponsor's ISS. [Vol. 44.9, p. 144.]

Section 8.4.1 Local effects of EMLA:

Application site adverse reactions were reported in 41% of the EMLA-treated patients the 12 single-dose studies. These included redness 20.9 %) burning sensation (16.7%) and edema (10.3%). The highest incidences of redness in EMLA-exposed patients were noted in the application time-response studies (29.8 %) and the uncontrolled studies (35.8%).Within the placebo-controlled studies, the EMLA patients showed redness (12.6%) and burning sensation (15.6%). For the placebo-exposed patients in these studies redness was 8.5% and burning sensation was 9.6%.

For EMLA-treated patients, there were only five adverse events reports that were not classified as application site disorders. These were symptoms from the nervous system (one report of faintness, one report of limb tremor), cardiovascular system, involving two vasovagal reactions, and one case of transient mucosal burning. In study 90EM11 an EMLA treated patient felt mildly faint 4 minutes after a lidocaine injection subsequent to EMLA removal. This may have been due to the epinephrine in the local anesthetic solution. In study 84EM07 an EMLA patient had limb tremor (described as slightly "shaky legs") after the operation but recovered within 15 minutes without any treatment. A second patient in this study had a mild vasovagal reaction (felt dizzy). [Vol. 44.3, p.105.] In study 84EM11 (an uncontrolled single dose study) a woman developed a vasovagal reaction and fainted after 4 g of EMLA had been applied for 65 minutes. There was no sign of systemic anesthetic toxicity and she recovered in a few minutes. [Vol. 44.9, p.135.] Of these reactions, it appears to this reviewer that only the transient transmucosal burning in Study 84EM06 appear to be possibly drug related. This last reaction was categorized as a peripheral nervous system reaction because the location was not specified. [Vol. 44.9, p. 119, 124-128.]

Section 8.4.2 Adverse Events by Gender

The sponsor's ISS is focused on the use of EMLA for application to genital mucous membranes primarily in women. Seven men included in these studies had EMLA applied to genital mucous membranes but were not included in the integrated safety data set. However, adverse event data was collected from them. The symptoms noted in both sexes were similar and included local redness, pallor and edema. [Vol. 44.9, p. 148.]

Section 8.4.3 Adverse Events by Age

The majority of patients in these studies were young adults, with a median age of 25. Pediatric clinical studies of EMLA Cream 5% on intact skin have been conducted, and an sNDA describing the use of EMLA on neonates has been approved (sNDA 010). [Vol. 44.9, p.143.]

Section 8.4.4 Adverse Events by Race

It should be noted that the majority of patients in these studies were Caucasian. There does not appear to be adequate data to determine if there is a difference in safety of EMLA Cream 5 % between the mucosa of Caucasians and any other race. There are no reports that topically applied local anesthetics on genital mucosa act differently in ethnically different populations. [Vol. 44.9, p.148.]

Section 8.4.5 Post-Marketing Experience

The sponsor estimates there have been approximately 75.5 million treatment days of post-marketing experience with this drug, on various types of tissues including the genital mucous membranes.

EMLA Cream has been marketed in Sweden since 1984 and has been approved in 63 countries. Approval for the use of EMLA Cream on genital mucosa has been granted in 47 countries

including Canada, France, and Sweden. {See table at the end of this section. Table was taken from sponsor's table 28, Vol.44.9, pp.154-155.] The sponsor makes the point that EMLA has never been removed from the market for safety or for any other reasons. There are no known long-term adverse experiences attributable to this of this drug.

During the time period April 1 1990 through March 31, 1998, a review of the world-wide Periodic Adverse Drug Experience Reports from the marketed use of EMLA Cream, reveals nothing significant apart from what is already included in the approved labeling. Nothing specific has been reported for mucous membranes,

The sponsor has provided a discussion of a literature search that described adverse events that were similar to those reported in this submission's ISS. Van Der Burght et al studied onset and duration of analgesia produced by EMLA to genital mucous membranes in female volunteers. There were no reports of discomfort or adverse events related to EMLA application. Frega et al reported on an active-control study of EMLA, in 90 male and 90 female patients, for anesthesia prior to laser removal of genital warts. Moderate erythema was noted in 21.1% of the males, and 25.5% of the females, while slight pallor and edema were noted in 11.1% of the males and 14.4% of the females. Sarkar et al. describes a placebo-controlled study of EMLA for laser vaporization of cervical pre-malignant conditions, where the majority of patients experienced no adverse reactions. Byrne et al. describes a study in which EMLA, applied as anesthesia prior to vulval biopsies, resulted in local erythema and edema in six out of ten patients. No adverse events were reported either by Stigliano et al. in a study comparing EMLA and lidocaine spray as anesthesia for office hysteroscopy, or by Sarkar in a pilot study of EMLA as anesthesia for carbon-dioxide treatment to the cervix. [Vol. 44.9, pp.153-156.]

Reviewer's Table 18. Registration status of EMLA Cream use on genital mucosa. See next page:

Country	Approval of EMLA Cream	Approved on genital mucous membranes
Argentina	1991	1991
Australia	1988	no
Austria	1996	1996
Bahrain	1994	yes
Belgium	1987	1989
Brazil	1994	yes
Canada	1990	1993
Chile	1994	-
China	1998	-
Colombia	1990	yes
Cyprus	1990	yes
Czech Republic	1997	1997
Denmark	1985	1985
Ecuador	1996	yes
El Salvador	1998	-
Estonia	1997	yes
Eire	1988	1992
Finland	1985	1990
France	1990	1997
Germany	1992	no
Greece	1989	1989
Guatemala	1998	-
Hong Kong	1986	-
Iceland	1987	submitted 1997
Indonesia	1998	1998
Israel	1989	yes
Italy	1993	1993
Jamaica	1997	yes
Jordan	1998	yes
Kuwait	1995	yes
Lebanon	1997	-
Lithuania	1997	1997
Luxembourg	1988	1989
Malaysia	1990	-
Mexico	1998	-
Netherlands	1987	1988
New Zealand	1986	no
Norway	1987	1989
Oman	1997	yes
Paraguay	1992	yes
Peru	1995	yes
Philippines	1984	-
Poland	1995	yes
Portugal	1996	1996
Rumania	1997	1997
Singapore	1991	1991
Slovenia	1995	yes
South Africa	1992	1992

Country	Approval of EMLA Cream	Approved on genital mucous membranes
South Korea	1994	yes
Spain	1996	1996
Sweden	1984	1985
Switzerland	1985	1993
Taiwan	1992	yes
Thailand	1987	yes
Trinidad & Tobago	1997	yes
Turkey	1997	1997
Uganda	1995	-
UK	1986	1990
United Arab Emirates	1996	yes
Uruguay	1994	yes
USA	1992	no
Vietnam	1996	-
Yugoslavia	1996	1996

- not submitted or no information available
yes approved, but approval date not available

Reviewer's Table 18. [Vol. 44.9, pp.154-155.]

SECTION 8.5 .....OTHER SAFETY FINDINGS

Section 8.5.1 Clinical Laboratory Evaluations

There were no clinical laboratory evaluations conducted during these studies. [Vol. 44.9, p.144.]

SECTION 8.6 .....DRUG-DRUG INTERACTIONS

No drug-drug interactions were reported during these studies. Concomitant medication usage was low, and reflected the normal range expected in an essentially healthy study population. The highest medication usage (forty-nine patients or 13%) used oral contraceptives which are considered unrelated to the use of EMLA. If concomitant local anesthetics were used, they were given only after recording of pain and local adverse events. [Vol. 44.9, p.144.]

SECTION 9.0 LABELING REVIEW

See Attachment A, Labeling Review.

SECTION 10.0 CONCLUSIONS

Study 90EM11 has shown EMLA to be effective as an adjunct to local anesthetic infiltration. Studies 84EM07 and 86EM07 have shown the effectiveness of EMLA as a sole anesthetic to be variable. As a result, EMLA Cream should be used with caution as sole anesthetic on genital mucous membranes. It should be noted that the results of the trials appear to contain only 378 evaluable EMLA patients for safety and 376 evaluable EMLA patients for efficacy.

It should again be noted that the sponsor reported no deaths, serious adverse events, or discontinuations during these trials. As noted in the previous label, there was a concern over safe dosing recommendations on mucous membranes based on the lack of adequate studies. It is this reviewer's opinion that this safety concern has been adequately addressed in this submission. It should also be noted, however, that in a subsequent submission (August 6,1999), the sponsor refers to a death in a patient of unknown age, and a case involving methemoglobinemia in a 3 month old infant. Both these cases appear to be linked to overdosage and, in the case of the death, use on a severely burned patient. Based on a review of the data submitted, EMLA appears to be reasonably safe when used as recommended.

SECTION 11.0 RECOMMENDATION

In the opinion of this reviewer, NDA19-941/SE-1, #011 efficacy supplement is approveable. EMLA is indicated for use as adjunctive treatment to local anesthetic infiltration. However, the efficacy of EMLA as sole anesthetic on genital mucous membranes is variable and should, therefore, be used with caution. After review of the safety data provided, and comments from other members of the review team, I feel this efficacy supplement is approveable provided appropriate labeling modifications to the draft labeling are instituted.

APPENDICES

/S/ /S/

Harold J. Blatt, D.D.S.

Division of Anesthetics, Critical Care, and Addiction Drug Products

January 7, 2000

ADDENDUM TO REVIEW

Note: Omitted in error in the Administrative History section was the following:

Efficacy supplement NDA 19-941/SE8-010 was approved on March 11,1999 for the indication of dermal anesthesia for topical use on intact skin in full term neonates (minimum gestation period 37 weeks).

Note: Trial 86EM07 was omitted in error from the main review and is attached here.

Study 84EM06 is an open-label, randomized, parallel group, active controlled study to compare EMLA Cream 5% and mepivacaine adrenaline 1% for cervical curettage. There were a total of 60 (30 in each group) female patients. The EMLA group received a single total dose of 10ml of EMLA applied to the lateral fornices for from 18 to 22 minutes. The control group received a total of 20ml mepivacaine adrenaline for paracervical blockade 9-21 minutes before the operation.
EFFICACY RESULTS: Score of pain on VAS and discomfort were significantly higher from the injections (pain 31, discomfort: 35) than from the cream application (pain: 2, discomfort: 5). No significant difference in pain or discomfort from the operation (EMLA pain: 19, discomfort: 21) (Control pain:21, discomfort: 18).
SAFETY RESULTS: EMLA group reported slight itching 3% and transient burning 30%.No local irritation in the control group but visual inspection showed blanching in 47%. No AEs reported in the EMLA group. In the control group tachycardia was reported in 5 patients, tinnitus in 1, and general weakness in 1. All reactions were transient and recovery was within 5 minutes without need of medical treatment.

Endpoints:

I. Patient assessment of pain and discomfort from application of cream of injection on 100 mm VAS.

II. Patient assessment of pain and discomfort from the curettage on a 100 mm VAS.

III. Patient assessment of anesthetic method. Would they consider this type of anesthesia for curettage again.

IV. Local reactions assessed by patient's comments and visual inspection.

/S/

Harold Blatt, D.D.S.

STATISTICAL REVIEW AND EVALUATION

NDA#:	19-941 SE2-011
Applicant:	Astra Pharmaceuticals, L.P.
Name of Drug:	EMLA Cream (lidocaine 2.5% and prilocaine 2.5%)
Indication:	Dermal analgesic for topical use on intact skin
Documents Reviewed:	Vol.44.1-Vol.44-9, dated March 29, 1999, and submission on Dec. 17, 1999 and Dec. 21, 1999 SAS Database dated May 20, 1999, received Sept. 22, 1999
Medical Officer:	Harold J. Blatt, D.D.S (HFD-170)
Medical Team Leader:	Bob Rappaport, M.D. (HFD-170)

This review has been discussed with the medical review team.

BACKGROUND

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) was approved on December 31, 1992 as "a topical anesthetic for use on normal intact skin for local analgesia." In March 1999, Astra Pharmaceuticals submitted "EMLA Cream" NDA efficacy supplement for review. It is intended to support the safe and effective use of EMLA as a topical anesthetic for superficial minor surgery of genital mucous membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes. This supplement NDA consists of 14 non-US clinical trials (four pivotal, six supportive, and four involving either a different concentration of EMLA (2%) or different indication), see Table 1.

This review pertains to four double-blind placebo-controlled studies and two open-label studies characterized by the sponsor as 'pivotal' studies. Among these six trials, four (86EM07, 86EM04:1, 83P026, and 84EM07) were indicated for superficial minor surgery, one (90EM11) for adjunct to infiltration, and one (84EM12) for other indications. The sponsor considered 86EM07, 86EM04:1, 83P026, and 90EM11 pivotal studies. In addition, the two open-label active control studies reported by the sponsor were summarized.

Keywords: Clinical study, NDA review.

Table 1. Summary of trials by study design and study indication

	Superficial Minor Surgery		Adjunct to infiltration	Other indications
	Pivotal	Supportive	**Pivotal**	
Placebo-controlled	86EM07*	84EM07*	90EM11*	84EM12*
Active-controlled		84EM06~ EM9404^		
Application time-response	86EM04:1# 83P026#	86EM12^		
Uncontrolled		86EM04:2~ 84EM11#		83P036#
Diff concentration or application schedule				89Li02 81P029

* randomized, double-blind, parallel group, and single center trial
~ open label, single center, parallel group comparison
^ open label, multi-center, randomized, parallel group comparison
# open label, single center, EMLA cream with different application times

SUPERFICIAL MINOR SURGERY INDICATION

STUDY 86EM07

This was a double-blind, placebo-controlled trial. Female patients receiving laser treatment of condylomata were randomized to receive local anesthesia with either 5g EMLA cream (n=60) or placebo cream (n=20) applied to the genital mucosa. The cream was evenly spread over the mucosal part of the vulva between 1 and 75 minutes before surgery. No premedication was given. A standardized area of 3x3cm surrounding at least one condyloma was treated with an intermittent CO2 laser pulse (0.2S) with a power density of about 600 w/cm^2 (17w, spot size 2mm). Patients were asked to rate the pain experienced from the laser treatment and also (when given) from the injection on a 100 mm Visual Analog Scale (VAS). Patients were to also rate the pain on a verbal scale as "none", "slight=quite tolerable", "moderate=not quite tolerable" or "severe=intolerable" and the need for supplementary analgesia.

The study objectives were to investigate the use of EMLA cream as local anesthesia for laser treatment of the female genital mucosa regarding (1) analgesic efficacy compared to placebo, (2) the minimum effective application time, and (3) any decrease in analgesic efficacy up to 75 minutes application time. In addition, the pain from injection of any additional analgesia in the EMLA and placebo groups was to be compared. Differences between groups were to be tested by a non-parametric method.

RESULTS

The sponsor reported that treatment groups were comparable with regard to both age and location of the test area (Table 2).

Table 2. The patients' age and the location of the test (3x3cm) area – 86EM07

	EMLA (n=60)	Placebo (n=20)
Age in years: median (range)	22.5 (18-55)	22.5 (17-45)
Location of warts: # of patients		
Vestibule	23 (38%)	7 (35%)
Labia minora	28 (47%)	16 (80%)
Labia minora, meatus	1 (2%)	-
Labia majora, interior	19 (32%)	3 (15%)

ANALGESIC EFFICACY

This reviewer confirmed the sponsor's report on the patients' assessment of 100mm Visual Analogue Scale (VAS) pain with 0 of no pain and 100 of worst pain: median 12 (range 0 to 96) in the EMLA arm and median 80 (range 34 to 100) in the placebo group. The differences in VAS pain without reference to the length of the application time was statistically significant ($p<0.0001$) using parametric or non-parametric approaches, see Figure 2 of the sponsor report.

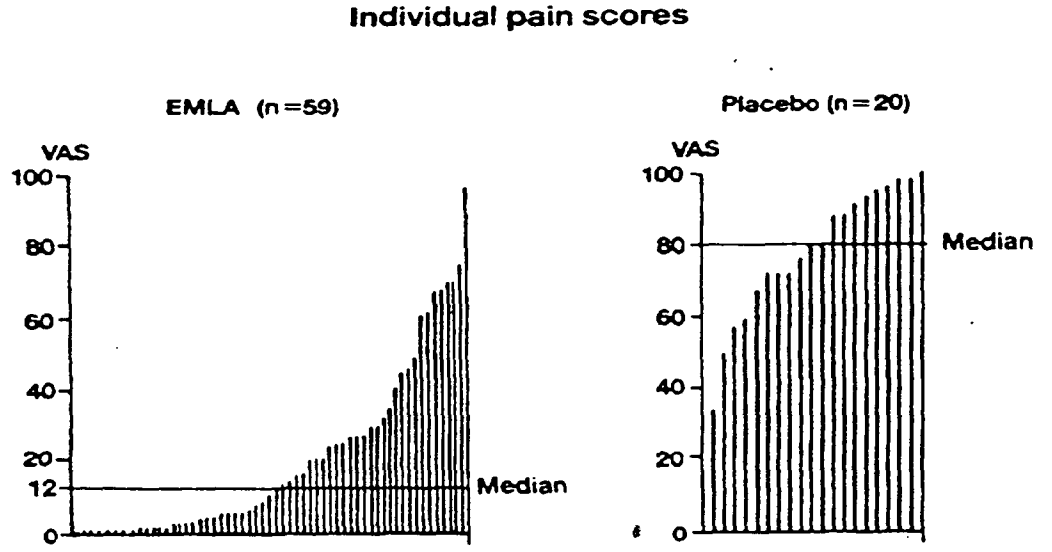


Figure 2. Individual pain scores (VAS) in the treatment groups arranged in increasing magnitude of the scores. The median score is indicated by a horizontal line.

The sponsor pre-specified that the comparison be made with application times longer than the minimum effective time, which was to be detected using the cusum technique, a method used to estimate when change of rate occurs which requires specification of an initial reference value. In addition, if an upper boundary of effective anesthesia was identified, the sponsor would restrict the comparison of VAS pain to include patients between the upper and lower boundaries in the

EMLA group. Separate analysis was also to be made between the placebo group and patients in the EMLA group with application times shorter than the minimal effective as well as longer than the upper boundary (if any). In the NDA report, the sponsor stated that the level of significance was adjusted according to Bonferroni. The differences between the groups with regard to analgesic efficacy were tested with the Mann-Whitney test (with variance corrected for ties where appropriate). The difference in the need for additional analgesia and the frequency of local reactions was tested with the two-sided Fisher exact test. The Wilcoxon paired-sample test was employed to compare the pain ratings between placebo and additional EMLA in the placebo group.

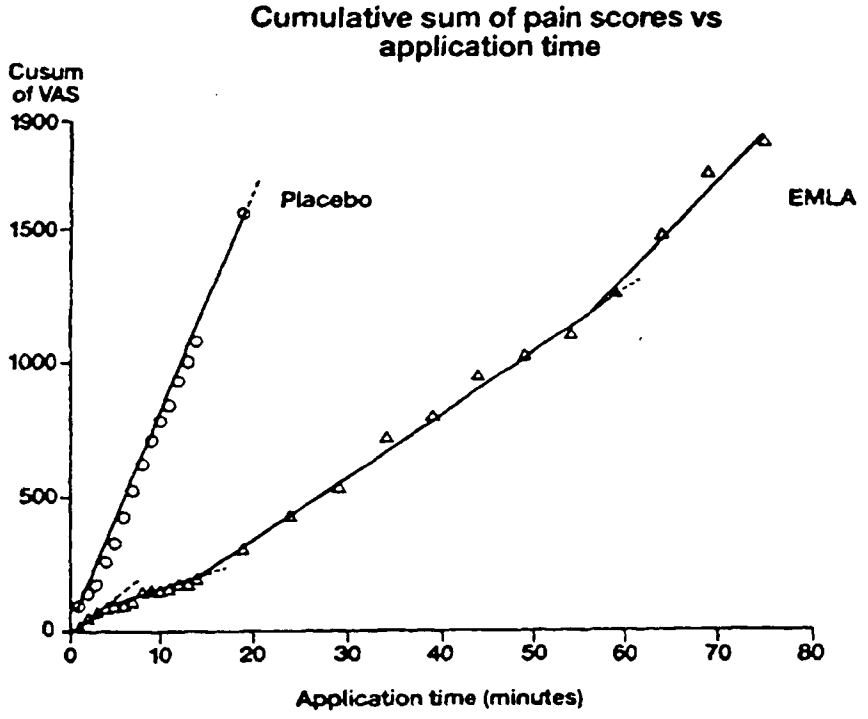


Figure 4. Cusum plot (enlargement of Figure 3). The horizontal trend in the EMLA curve between 5 and 15 minutes was obscured by a VAS rating of 61 from one patient treated for 8 minutes (Pat. No. 79).

According to the sponsor, "the cusum plot (Figure 4 of the sponsor) of the EMLA group showed that effective anesthesia was obtained after only 4-5 minutes' application of the anesthetic cream. There was a second shift in trend after about 15-20 minutes, and a further change after 50-60 minutes, indicating increases in pain scores." The distribution of the need for additional analgesia according to application time was in agreement with the cusum plot.

The sponsor claimed that the upper time-boundary of the most effective anesthesia in the EMLA group was found to be 15-20 minutes and used 5 minutes as the lower boundary and 16 minutes as the upper for the comparison of VAS pain between EMLA and placebo (Table 3).

Table 3. The sponsor's results on VAS pain by application time below, within and above the most efficient time interval - 86EM07

	EMLA (n=60)		Placebo (n=20)	p-value
	N*	median (range)		
Application time: 1-4 minutes	8	20.5 (0, 67)	80 (34, 100)	<0.01
Application time: 5-16 minutes	21	3 (0, 61)		<0.01
Application time: 17-75 minutes	30	20 (0, 96)		<0.01

* the sponsor excluded one patient in this analysis

Median cream application times were 15 minutes (range: 1-71 minutes) in the EMLA treated group and 10.5 minutes (range: 1-61 minutes) in the placebo treated group.

REVIEWER'S COMMENTS

The cusum method may result in slightly different cutoff values depending on what the initial reference value was. This reviewer performed statistical analyses on the primary efficacy outcome of VAS pain by various cutoffs of the EMLA application times. Considering that the lower boundary of 4-5 minutes, it appeared that the robustness of the significant results on less pain in favor of in the EMLA group compared to the placebo group was held even when the upper boundary of 55-60 minutes was applied. The verbal pain assessment showed that 20% (9/45) patients in EMLA and 100% (13/13) patients in placebo reported moderate to severe pain.

According to the sponsor, 15 placebo treated patients were given additional EMLA and rated the VAS pain from the continued treatment with a median of 3 (range 0-33), significantly ($p<0.01$) less painful than their first treatment (placebo) with a median of 88. The median application time of additional EMLA cream was 5 minutes.

STUDY 84EM07

This was a double-blind, placebo-controlled, single dose trial to evaluate the analgesic effect of EMLA as a topical anesthetic for biopsy and cervical curettage. Female patients with cervical intraepithelial neoplasia, scheduled for cervical curettage on a day-patient basis and did not have suspected hypersensitivity to local anesthetics of the amide type and operations where general anesthesia was indicated, were randomized to receive either 10ml EMLA cream 5% (n=30) or placebo (n=30). After colposcopy, 10ml cream was applied in the lateral fornices, 5ml on each side. Towards the end of the 20 minutes application time, patients were asked about any local irritation caused by the cream, and the portio and vagina were examined for any local adverse reactions. After completion of cervical curettage and biopsy operation, patients were asked to assess the pain and discomfort on VAS and whether she would consider using the same type of cream in the event of a future operation. The gynecologists were to make an overall clinical assessment of the procedures on a 4-point scale of excellent, satisfactory, only just acceptable or unacceptable. The protocol called for non-parametric statistical methods to test hypotheses about parameters.

RESULTS

A total of 60 female patients aged 22 and 56 years were studied. In the EMLA arm, 53% of the patients were nulliparous and 40% had previously undergone some form of gynecological operation. The corresponding figures were 33% and 66% in placebo.

EFFICACY

The sponsor reported the results of the efficacy evaluation using t-test, Chi-square and the 2-tailed Fisher exact test as follows. The mean pain score on the VAS was 21 in EMLA and 28 in placebo, not statistically significantly different. The mean discomfort score on the VAS was 24 in EMLA and 38 in placebo ($p<0.05$). Eighty percent of the patients in EMLA and 57% of the patients in placebo stated that they would consider using the same cream in any future operation ($p=0.053$); the gynecologist's subjective evaluation of the procedures was in favor of EMLA ($p<0.01$). Figures 1 and 2 of the sponsor gave graphical presentations of individual pain and discomfort scores on the VAS in order of increasing magnitude, respectively.

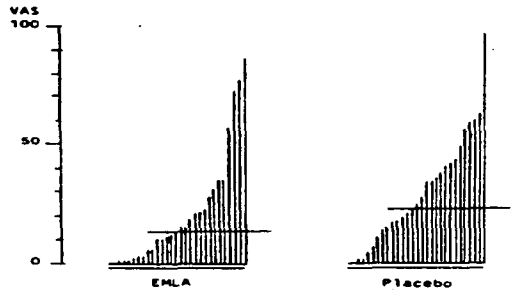


Figure 1. Individual pain scores on the VAS, in order of increasing magnitude.

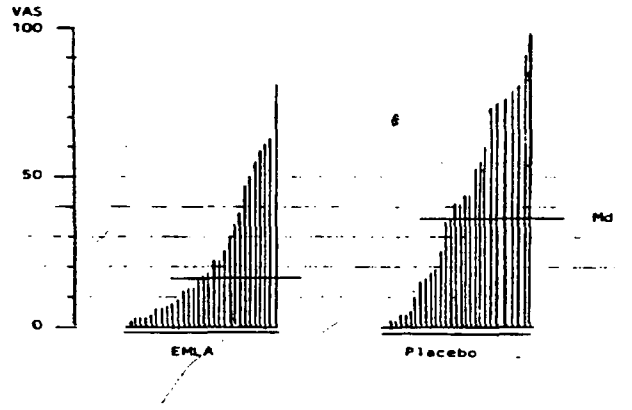


Figure 2. Individual discomfort scores on the VAS, in order of increasing magnitude.

REVIEWER'S EVALUATION AND COMMENTS

The protocol called for non-parametric analyses of clinical efficacy outcomes. This reviewer performed the protocol specified analyses, and tabulated results from this reviewer (Wilcoxon rank sum test) and those from the sponsor (t-test), as shown in Table 4 below.

Pain and discomfort on VAS – when the protocol specified non-parametric approach was used, results of Wilcoxon rank sum test showed that there was no statistically significant difference in median pain on VAS between EMLA (median: 14, range 0 to 87) and placebo (median: 24, range 0 to 97), p=0.104. The sponsor's report on comparison of VAS pain between EMLA and placebo overall and its subgroups of para=0 and para>0 were consistent in terms of no statistical significance with either the t-test reported in the NDA submission or the non-parametric test specified in the protocol. With the efficacy outcome of VAS discomfort, inconsistent results were found. That is, no statistical significance was shown using the Wilcoxon rank sum test (p=0.120), but a borderline nominal significance (p=0.049) was found with the t-test. Similar results were seen in the subgroup of para=0.

Table 4. Reviewer's analysis of efficacy outcomes – 84EM07

	EMLA (n=30) n ave(sd) med(range)	Placebo (n=30) n ave(sd) med(range)	p-value (report)	p-value (protocol)
VAS pain	30 21(24), 14(0, 87)	30 29(23), 24(0, 97)	0.212	**0.104***
In para=0	16 24(25), 18(0, 77)	10 34(17), 37(11, 59)	0.289	0.147
In para>0	14 18(22), 12(0, 87)	20 26(26), 21(0, 97)	0.316	0.318
VAS discomfort	30 24(22), 17(0, 81)	30 38(30), 39(0, 99)	0.049	**0.120***
In para=0	16 28(27), 18(0, 81)	10 53(25), 54(0, 81)	0.029	0.058
In para>0	14 19(16), 17(3, 50)	20 31(31), 19(0, 99)	0.217	0.575
			Chi-sqr	Fisher exact test
same cream-Y^	24 (80%)	17 (57%)	0.052	0.095
Physician evaluation	20 (67%)	11 (37%)	0.020	0.038

* protocol specified analysis performed by this reviewer.
^ number of patients consider using the same cream in any future operation.
~ number of patients physicians considered as excellent in the overall clinical assessment.

Attitude towards the cream – statistical significance at 2-sided 0.05 level was not reached with the Chi-square test (p=0.052) and the Fisher's exact test (p=0.095).

Overall clinical assessment - 67% of EMLA treated patients and 37% of placebo treated patients were considered as excellent in the overall clinical assessment. Results from the Chi-square test (p=0.020) and the Fisher's exact test (p=0.038) appeared to be nominally significant.

Based on the protocol specified statistical plan to achieve its objective of analgesic effect of EMLA, pain and discomfort on VAS, and % of patients considering use of the same cream in any future operation were not shown to be statistically significantly different between the treatment groups, although % of patients considered as excellent in the overall pain/discomfort clinical assessment was in favor of EMLA. Overall efficacy or individual efficacy with multiplicity adjustment were not shown.

STUDY 84EM06

This was a single center randomized open-label comparison of EMLA cream 5% and PCB (1% mepivacaine adenaline as anesthetic agents, the active-control) for cervical currettage. A total of 60 female patients scheduled for cervical curettage due to cervical intraepithelial neoplasia (CIN) on an out-patient basis were included in this study with 30 patients in each treatment group. Since it was an open-label comparison, results were likely to be subjective to bias, particularly when the efficacy measurements were somewhat subjective. This reviewer just summarizes the sponsor's results for informational purpose.

The sponsor reported that scores of pain on VAS, as well as scores of discomfort, were significantly higher from the injections (pain:31, discomfort:35) than from the cream application (pain:2, discomfort:5), $p<0.001$; there was no significant difference in scores of pain and discomfort from the operation between the two groups (EMLA: mean pain=19, mean discomfort=21; PCB: mean pain=16, mean discomfort=18); the majority of the patients in both groups stated that they would choose the same kind of anesthesia for a future operation; no adverse events were reported from the EMLA group. In the PCB group, tachycardia was seen in 5 patients, tinnitus in 1 and general weakness in 1. All reactions were transient and the patients recovered within 5 minutes without any need for medical treatment.

STUDY EM9404

This was a multi-center randomized open-label comparison of EMLA cream (n=31) and infiltration anesthesia (Xylocaine, the active control, n=32) for biopsy for the genital mucosa. The objective was to assess analgesic effect and adverse reactions of EMLA 5% cream. A total of 61 patients, excluding 2 patients due to wrong order of randomization, aged 18 to 81 years, were available for efficacy evaluation. The sponsor's results of this open-label active-control comparison were summarized. It is noted that results of an open-label study are likely to be subjective to bias, particularly when the efficacy measurements were somewhat subjective.

The sponsor reported that there was a significant difference in EMLA's favor with regards to pain scores related to the anesthetic procedure ($p<0.05$), and in Xylocaine, an advantage with regards to pain scores related to the biopsy ($p<0.05$); 5 patients in EMLA and 1 patient in Xylocaine received additional infiltration of Xylocaine; combined median pain score (anesthetic procedure + biopsy) were less in EMLA (2.5) than in Xylocaine (3). There was no significant difference between these two median scores. Local reactions were more numerous in EMLA (n=19) compared to Xylocaine (n=8) ($p<0.05$); pallor and burning sensation were the most frequent reactions in the EMLA treated group.

STUDY 86EM04:1

This was an open label trial to evaluate the time of onset of local anesthesia by EMLA cream of the genital mucosa and the analgesic efficacy for cautery of genital warts.

REVIEWER'S COMMENTS

The information summarized is for reference only. The protocol did not have a statistical analysis method defined for definitive comparison.

In a pilot study, all 10 patients were anesthetized within 5-7 minutes; 9/10 patients rated the pain from the cautery as none or slight. In the main study, 42 women were given a dose of 5g EMLA for 10, 15, or 20 minutes. The pain from the cautery was rated as either none or slight by 92% (11/12) in the 10 minute group, 67% (12/18) in the 15 minute group, and 50% (5/10) in the 20 minute group. Additional analgesia was given to 1/12 patients in the 10 minute group, 6/18 in the 15 minute group, and 5/10 patients in the 20 minute group. The sponsor concluded that the time of onset of anesthesia by EMLA cream of the genital mucosa was 5-7 minutes, and the anesthesia was sufficient for cautery of condylomata in 90% of the patients after the application of EMLA for 5-10 minutes.

STUDY 83P026

The study was originally planned to be a double-blind, randomized study for comparisons of 2% and 5% lidocaine-prilocaine cream (EMLA) as anesthesia for cervical curettage. An amendment of research protocol was attached in the NDA report. From this amendment, due to no convincing evidence regarding the most efficacious application-time from the initial pilot study of 10 patients and the pharmaceutical properties of the cream formulation such as pH and viscosity were thought to have an influence, the pilot study was extended. Altogether 39 patients had been treated when the study was concluded. The amendment stated that "The main part of the study (comparison between 2% and 5% creams) was postponed and instead a new study comparing EMLA with paracertival blockage will be initiated."

REVIEWER'S COMMENTS

From the submitted NDA report, this was a single dose open non-randomized study, which evaluated if 10ml EMLA 5% has sufficient analgesia for cervical curettage. It appeared that not only was the trial design drastically different from originally planned double-blind comparison trial, but also pilot study indicated no convincing evidence on the most efficacious application time. This open label non-randomized study could at best be considered as descriptive only. A total of 39 female patients aged 18 to 47 years received 5% creams with pH 8.5 or 9.5. Three different application times studied were 10, 20 and 60 minutes. The sponsor stated that median pain score on VAS was 20mm in the 10 minute group, 15mm in the 20 minute group, and 20mm in the 60 minute group.

According to the sponsor submission dated Dec. 17, 1999 and January 11, 2000, no patients from the 39 patients evaluated received 2% EMLA cream. The protocol specified comparison between 2% and 5% EMLA cream cannot be made. It appeared that the initial pilot study included 3 patients and the total 39 patients were considered as an extended pilot study.

ADJUNCT TO INFILTRATION

STUDY 90EM11

This double-blind, placebo-controlled study evaluated the analgesic effect of EMLA 5% cream, compared to placebo, as a pre-medication for local infiltration of the genital mucosa of women. The VAS score was the efficacy parameter. Non-parametric methods were to be used to test the difference in pain between the EMLA and the placebo treated groups. The study was performed over a 14 months period from February 1991 to April 1992.

Eligible female patients aged 18 years and older, scheduled for infiltration prior to either a biopsy or other surgical procedure of the external vulva or the genital mucosa, were randomized to receive either EMLA cream 5% (n=21) or placebo (n=23). The cream was applied for a period of 6 to 10 minutes. Following removal of the cream, Xylocaine infiltration was performed. The degree of pain from the infiltration procedure was measured, by the patient, using a 100mm VAS and a four point verbal rating scale (VRS).

RESULTS

A total of 44 patients received the study medication. There were no statistically significant differences in age distribution between EMLA [median: 36 years (range: 19 to 63)] and placebo [median: 29 years (range: 18 to 76)].

EFFICACY

The protocol called for analysis of efficacy using non-parametric approaches. The sponsor reported parametric results (t-test) instead.

REVIEWER'S EVALUATION AND COMMENTS

This reviewer performed the statistical analyses using the protocol specified analysis (see Wilcoxon Rank Sum p-value column) and tabulated the NDA report (see t-test p-value column), as shown in Table 5.

Table 5. Reviewer's analysis of efficacy outcomes – 90EM11

	EMLA (n=21) ave(sd) med(range)	Placebo (n=23) ave(sd) med(range)	p-value (t-test)	p-value (Wilcoxon RS)
Age in years	37(14), 36(19,63)	34(15), 29(18, 76)	0.539	0.451
VAS pain	23(19), 25(1, 64)	43(24), 39(7, 88)	0.004	0.005
			Chi-square	Fisher's exact
VRS pain^	5 (24%)	12 (52%)	0.056	0.069

^ number of patients verbally rated moderate to severe pain with use of the cream

In this study, results of both parametric and non-parametric analyses gave consistent statistical evidence for treatment efficacy. A significant improvement in pain measured by VAS was seen in the EMLA treated patients [median: 25mm (range 1 to 64)] compared to the placebo treated

patients [median: 39mm (range 7 to 88)], p=0.005, Wilcoxon rank sum test. However, when pain was measured by verbal rating scale of 0 (none) to 3 (severe pain), the numerical result indicated that half as much of the EMLA treated patients [EMLA (24%) and placebo (52%)] experiencing moderate to severe pain. Such difference was not statistically significant (p=0.069, Fishers' Exact test). On the average, patients experienced less pain with EMLA than with placebo.

The sponsor submitted two electronic data files, USDATA and POOLDATA, in which treatment codes were reversed. This reviewer inquired an explanation of the inconsistency. Per sponsor submission dated Dec. 21, 1999, it appeared that electronic datasets from studies entered in Sweden (84EM07, 84EM12, 86EM07), Canada (90EM11), and France (EM9404) were merged into a standard data format, i.e., USDATA, to be transferred to Astra Pain Control, Inc. for the integrated safety analysis (ISS). According to the sponsor, the data manager merged incorrectly the data tables containing patient data with the table containing randomization code. The sponsor stated that this was corrected in the POOLDATA utilized for the ISS analysis, and that the treatment assignments for patients in double-blind studies in the POOLDATA are entirely in agreement with the treatment assignments in the randomization lists. If the randomization list submitted by the sponsor is correct, this reviewer verified that treatment assignment in the POOLDATA is identical to the randomization list.

OTHER INDICATIONS

STUDY 84EM12

This double-blind, placebo-controlled study evaluated the analgesic effect of topical application of EMLA cream 5% in comparison with placebo in women undergoing removal and/or insertion of intrauterine device (IUD).

Eligible female patients aged 18 years and older, undergoing removal and/or inserting of IUD and not hypersensitive to local anesthetics of the amide type and/or not had had surgery to the cervix, were randomized to receive either EMLA cream 5% (n=23) or placebo (n=23). The cream was applied for a period of 20 minutes. Following removal of the cream, the cervix and vagina were examined for any local adverse reaction. If an IUD was in situ, it was removed. The uterine cavity was sounded to determine its depth, after which an IUD of appropriate type was inserted. After completion of procedure(s), patients made assessments of pain associated with the removal and/or insertion of the device(s) by means of VAS. Those patients who had previously experienced an IUD insertion were asked to retrospectively assess the pain on a 4-point verbal scale and to compare present with past pain. The physician made an overall clinical assessment of the procedure on a 4-point verbal scale (excellent, satisfactory, only just acceptable or unacceptable. The protocol said, "Statistical methods will be used to test for the significance of differences between treatment groups."

REULSTS

A total of 44 patients received the study medication. Median ages were 29 years (range: 17 to 37) in EMLA and 32 years (range: 18 to 44) in placebo; 34% in EMLA and 38% in placebo were

nulliparous; 70% in EMLA and 67% in placebo had previously had an IUD inserted; and 43% of the patients in each group already had an IUD removed before the insertion of the new device.

EFFICACY

The sponsor excluded three patients (#114, #216, and #217) from efficacy evaluation and reported that (1) mean score on the VAS for pain from removal of the IUD device was 32mm in EMLA (n=9) and 29mm in placebo (n=10) (not significant), and (2) mean score for pain from insertion of the device was 20mm in EMLA (n=23) and 15mm in placebo (n=20) (not significant).

REVIEWER'S EVALUATION AND COMMENTS

This reviewer performed an intent-to-treat analysis. Results are summarized in Table 6. Although there was no statistically significant difference in pain scores on VAS between EMLA and placebo at the removal and insertion of the IUD. It is noted that EMLA treated patients appeared to show numerically worse pain than placebo treated patients in both VAS pain and VRS pain.

Table 6. Reviewer's analysis of efficacy outcomes – 84EM12

	EMLA (n=23) n ave(sd) med(range)	Placebo (n=23) n ave(sd) med(range)	p-value (t-test)	p-value (Wilcoxon RS)
Age in years	23 28(6), 29(17,37)	23 31(7), 32(18, 44)	0.073	0.061
VAS pain^	23 20(20), 18(0, 79)	23 14(16), 8.5(0, 57)	0.277	0.384
VRS pain~	9 32(22), 25(0, 62)	12 27(18), 25(3, 59)	0.593	0.749
	# (%)	# (%)	Chi-square	Fisher exact
Para	8 (35%)	9 (39%)	0.760	1.000

^ VAS pain from insertion of the device
~ VRS pain from removal of the device

SUMMARY

This reviewer summarized the efficacy evaluation of pain on VAS from the four double-blind placebo controlled trials. From Table 7, for the indication to support topical analgesic effect in patients receiving superficial minor surgery, improvement on VAS pain was supported by Trials 86EM07 ($p<0.01$), however, Trial 84EM07 only showed a numerical difference in favor of EMLA cream. Improvement on VAS pain was also supported by Trial 90EM11 ($p=0.005$) designed for patients receiving EMLA cream adjunct to infiltration. As for "other indications," Trial 84EM12 showed a numerical difference in favor of placebo cream.

Table 7. Summary of VAS pain from double-blind randomized placebo controlled trials

	EMLA N Med (range)	Placebo N Med (range)	p-value*
86EM07	21 3 (0, 61)	20 80 (34, 100)	<0.01
84EM07	30 14 (0, 87)	30 24 (0, 97)	0.212
90EM11	21 25 (1, 64)	23 39 (7, 88)	0.005
84EM12	23 18 (0, 79)	23 8.5 (0, 57)	0.387

* Wilcoxon Rank Sum Test

CONCLUSION

Of the 14 non-US clinical trials submitted for review, this reviewer evaluated pivotal trials and double-blind, randomized, placebo-controlled trials. Analgesic effect was shown in one study (86EM07) treating patients undergoing superficial minor surgery but was not confirmed by the other double-blind placebo controlled study (84EM07). Such effect was shown in 90EM11 for treating patients receiving EMLA cream as an adjunct to infiltration assuming that the randomization list provided by the sponsor is correct. One open label study was originally designed to be a double-blind, randomized, comparison between 2% and 5% EMLA. The trial was changed to open-label design of 5% EMLA with different application times. A major reason for this trial's switching the design was due to no convincing evidence found in the pilot study of 3 patients all receiving 5% EMLA.

Overall, for superficial minor surgery indication, one of two double-blind randomized controlled trials appeared to show analgesic efficacy in use of 5% EMLA cream compared to placebo. On the other hand, the only double-blind randomized controlled trial in support for adjunct to infiltration showed analgesic efficacy in use of 5% EMLA cream compared to placebo.

/S/

Sue-Jane Wang, Ph.D. Jan. 14 2000
Mathematical Statistician

Concur: Dr. T. Permutt /S/

cc:
NDA#19-941 SE2-011
HFD-170/CMcCormick/BRappaport/HBlatt
HFD-170/Ms Milstein
HFD-344/Dr. Barton
HFD-715/Division File, Nevius/Welch/Permutt/Wang

SWANG/827-3089/January 7, 2000/emla.nda
This document consists of 13 pages, which includes 7 tables and 4 sponsor figures.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 19-941 SE1-011 **Submission Date:** March 29, 1999
Drug Name, Dose and Formulation: EMLA® Cream 5% (lidocaine 2.5% and prilocaine 2.5%)
Sponsor: Astra Pharmaceuticals, L. P. Wayne, PA 19087-5677
Type of Submission: NDA Supplement **Reviewer:** Shinja R. Kim, Ph.D.

SYNOPSIS: EMLA® Cream was approved on December 31, 1992 as "a topical anesthetic for use on normal intact skin for local analgesia". The current package insert also states that "EMLA is not recommended for use on mucous membranes. Safe dosing recommendations for use on mucous membranes cannot be made because it has not been studied adequately." The purpose of this supplemental application is to provide data, which supports the safety and efficacy of EMLA Cream as a topical anesthetic indicated for superficial minor surgery of genital mucous membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes.

EMLA® cream 5 % is an oil-in-water emulsion of eutectic mixture, contains lidocaine 25 mg and prilocaine 25 mg per gram. Lidocaine and prilocaine have been used as local anesthetics for many years, and their human pharmacological, pharmacokinetic and toxicological properties are well characterized. The occurrence of systemic CNS toxicity from lidocaine and prilocaine is related to peak plasma levels of the anesthetics. Initial signs of toxicity such as lightheadedness and dizziness have been reported at venous plasma levels of either anesthetic above 5-6 μg/ml. The recommended dose of EMLA® cream 5 % applied to genital mucous membranes for optimal anesthetic efficacy is 5-10 g and the recommended application time on mucous membranes is 5-10 minutes.

The pharmacokinetic (PK) objective of the clinical studies (there are 3 PK studies) has been to assess safety in terms of the maximum plasma concentration (C_{max}) of lidocaine and prilocaine resulting from the application of EMLA® cream 2 % or 5 % to genital skin or mucous membranes in adults. The time (t_{max}) to reach C_{max} was also assessed. Additionally, in one study, the primary objective was to investigate the systemic bioavailability of lidocaine and prilocaine.

The concentrations of lidocaine and prilocaine obtained after the topical application of 0.3-10 g (7.5-250 mg each of lidocaine and prilocaine base) EMLA® cream 5 % to the genital skin or mucosa of the adult for up to 69 minutes are well below concentrations (the highest individual concentration achieved in the plasma was 641 for lidocaine and 346 ng/ml for prilocaine) anticipated to give rise to systemic toxicity. Thus, the pharmacokinetic studies conducted by the sponsor (although has less than ideal assay information) support the approval of this submission.

COMMENT: Analytical methods reported by the Astra Lakemedel AB, which was employed to assay plasma concentrations of lidocaine and prilocaine in 3-PK studies were less than complete (but the report by TSI, used for BA assessment, was adequate). In future submissions, the sponsor should provide assay methodology as well as validation reports.

RECOMMENDATION: The supplement SE1-011 to NDA 19-941 is acceptable from the Clinical Pharmacology and the Biopharmaceutics perspective. The above comment and labeling comment on page 6 should be conveyed to the sponsor.

/S/

Shinja R. Kim, Ph.D., DPE II

/S/ 01/21/2000

RD/FT Ramana Uppoor, Ph.D.

cc: NDA (19-941), HFD-170 (Divisional File; Chamberlin, Blatt), HFD-850 (Lesko), HFD-870 (HuangS, Uppoor, Kim), CDR (Barbara Murphy)

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BACKGROUND

To assess safety margins, drug concentrations in the systemic blood are compared with estimate of threshold values associated with the toxicity, primarily CNS and/or the cardiovascular system; therefore, C_{max} and t_{max} are useful parameters in making clinically relevant comparisons with respect to plasma concentration which reveal CNS/cardiovascular toxicity. The range of potential CNS toxicity of lidocaine is reported to be between 5-10 µg/ml. Similarly, for the prilocaine, the CNS toxicity occurs when the dose exceeds approximately 600 mg in adults (concentration at about 5-6 µg/ml). It is generally assumed that the systemic absorption from topical application is higher when it is applied to mucous membranes than to the skin due to the absence of straum corneum and a higher tissue perfusion with the former for any given application time. Additionally, contrary to the skin, application of the EMLA cream on the mucous membranes covering the cream with an adhesive dressing is not necessary.

Some basic pharmacokinetic parameters for lidocaine and prilocaine in adults are available. For lidocaine, the systemic clearance, volume of distribution, and the terminal half-life following an intravenous dosing and in vitro plasma protein binding

Lidocaine is metabolized by liver microsomes and the primary pathway in humans is N-dealkylation to monoethylglycinexylidide (MEGX), followed by hydrolysis to 2,6-xylidine and then hydroxylation to 4-hydroxy-2,6-xylidine. Metabolism of prilocaine to *o*-toluidine and subsequent N-hydroxylation of this product is responsible for methemoglobinemia (at doses above 600 mg).

Studies with EMLA, 81P029, 83P026 and 83P036, explored the (early phase) anesthetic efficacy and safety (and 'dose selection') of different concentrations (2% and 5%) and different application times (10, 20 and 60 minutes) of the drug for the indications of cervical curettage, cervical biopsy and vacuum abortion. The doses used in females were 5 g of EMLA® 2 % (81P029), which equals to 50 mg each of lidocaine and prilocaine base and 10 g of EMLA® 5 % (83P026 and 83P036) corresponding to 250 mg each of lidocaine and prilocaine base.

OVERVIEW OF PHARMACOKINETICS:

81PO29 was an open-label nonrandomized study in 31 patients who underwent cervical curettage (n=26) or vacuum abortion (n=4) who received 5 g of EMLA® cream 2 %-corresponding to 50 mg each of lidocaine and prilocaine base. The dose was applied in the vaginal fornices and in the cervical canal. Venous blood samples were taken at appropriate times (up to 90 minutes after the dose) from the first ten patients enrolled. Since this study did not use the marketed strength, the study conclusions are not useful for this supplement.

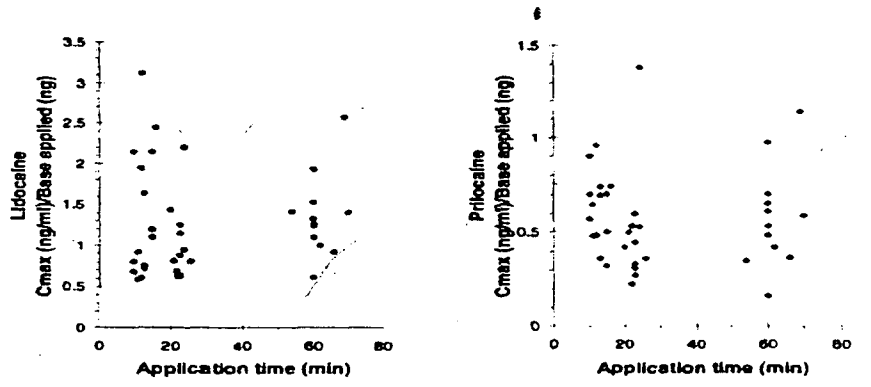
83PO26 was an open-label nonrandomized study in 39 patients scheduled for cervical curettage. The EMLA® cream 5% was applied in the fornices, 5 g on either side. It was washed away after 10, 20 or 60 minutes. Venous blood samples were taken from 9 out of 10 patients in the 60-minute group (sampling problems were encountered in one patient) at appropriate times up to 90 minutes after application of the cream. It is noteworthy that C_{max} and t_{max} values reported could be underestimating the true values, judged by the trend of increasing concentrations at the last sampling time (*i.e.*, plasma concentration was the highest at 90 minutes, the last sampling time point).

A third open-label nonrandomized study (**83PO36**), comprised 20 patients scheduled for vacuum abortion. In all patients the total volume of EMLA® 5% used was 10 g (250 mg each of lidocaine and prilocaine base). Either the entire dose of 10 g was applied in the fornices only (5 g on each side) or 3.5 g was applied bilaterally in the fornices and 3 g in the cervical canal, utilizing three target application times, 10, 20 or 60 minutes. In the first group of patients (n=6), the average application time was 11 minutes and the cream was applied in the fornices. In the second group, the average application time was 23 minutes and the cream was applied either in the fornices only (n=7), or in both the fornices and the cervical canal (n=4). Finally, in the third group (n=3), the cream was applied in both the fornices and the cervical canal for an average time of 63 minutes. Venous blood samples were taken at appropriate times up to 90, 120 and 180 minutes after the start of cream application in the 1st, 2nd and 3rd group, respectively. The results from all these 3 studies are summarized in the Table below:

	Lidocaine		Prilocaine	
Application Site (average time, min)	C_{max} (ng/ml) Mean ± SD (range)	t_{max} (min) Mean ± SD (range)	C_{max} (ng/ml) Mean ± SD (range)	t_{max} (min) Mean ± SD (range)
83PO26 Fornix (60)	130 ± 141 (155-641)	77 ± 16 (61-91)	158 ± 73 (40-286)	87 ± 10 (61-91)
83PO36 Fornix (11)	181 ± 32 (148-231)	36 ± 13 (21-60)	148 ± 25 (119-175)	36 ± 13 (21-60)
Fornix (23)	201 ± 45 (157-288)	58 ± 31 (30-125)	94 ± 29 (56-133)	43 ± 8 (30-51)
Fornix + Cervix (23)	315 ± 169 (158-549)	40 ± 11 (30-53)	178 ± 116 (83-346)	44 ± 10 (30-53)
Fornix + Cervix (63)	313 ± 69 (233-355)	97 ± 24 (74-121)	109 ± 34 (87-148)	68 ± 25 (45-95)
81PO29** Fornix + Cervix (14)	90 ± 35 (38-156)	52 ± 24 (30-90)	31 ± 11 (16-48)	57 ± 21 (30-90)

** 2% cream

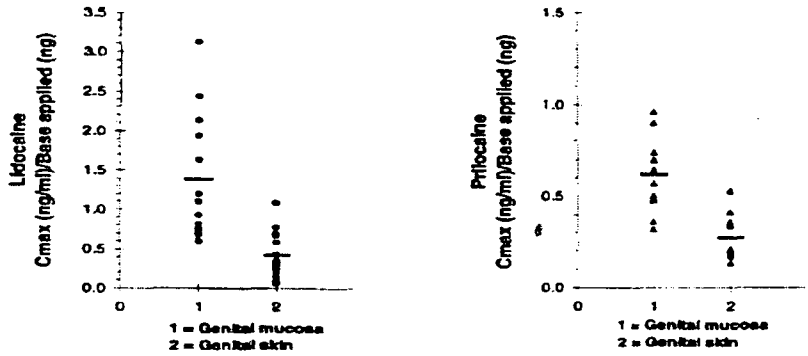
Dose corrected C_{max} of lidocaine (left graph) and prilocaine (right graph) obtained after varying application times to genital mucous membranes of EMLA cream 2 and 5% is shown below: it appears that there is no increase in dose-corrected C_{max} with increasing lengths of exposure to mucosa.



Bioavailability (93EML18) assessments: The bioavailability (BA) of EMLA cream 5 % was investigated in 20 male patients scheduled for removal of genital warts. Of the 20 patients entered in the study, 18 were assessable for lidocaine and 12 for prilocaine BA estimation. In the remaining patients, concentrations were below the ELOQ (Experimental Limit of Quantitation) of both assays (2.5 ng/ml). Two of these patients had concentrations below the ELOQ after the intravenous prilocaine dose. The application time of the cream was 15 minutes in all patients. One patient had the cream applied to the glans (considered the skin), while all the other patients had the cream applied to genital skin, the shaft of the penis. The results are summarized in the Table below:

Parameter	Lidocaine mean±SD (min-max) n = 18	Prilocaine mean±SD (min-max) n = 18
EMLA		
Cream (g)	1.0±0.9 (0.3–3.3)	0.7±0.5 (0.3–3.3)
Base (mg)	24.2±23.6 (7.5–82.5)	16.7±12.7 (7.5–55)
Application time (min)	15	15
Site	(Genital skin)	(Genital skin)
$AUC_{0-\infty}$ (ng/mL•h)	32.4±14.5 (8.2-53.4)	12.9±5.5 (7.4-26.8)
C_{max} (ng/mL)	6.6±3.8 (2.5-16.2)	3.7±1.4 (2.5-7.3)
t_{max} (min)	95±47 (45-180)	79±52 (20-180)
Residual AUC (% of $AUC_{0-\infty}$)	47±20 (20-87)	67±22 (22-96)
F (%)	14±10 (2-39)	6±3 (3-14)

Dose-corrected C_{max} of lidocaine (left graph) and prilocaine (right graph), for genital mucosa *vs.* skin obtained after application of EMLA cream 2 and 5% for 10-15 minutes is shown below. Bars indicate the mean value for each group.



Approximately twice as high dose-corrected C_{max} obtained after application to genital mucosa, as compared to application to genital skin suggests that BA is to be expected to follow the same pattern.

CONCLUSION:

The concentrations of lidocaine and prilocaine obtained after the topical application of 0.3-10 g (7.5-250 mg each of lidocaine and prilocaine base) EMLA® cream 5 % to the genital skin or mucosa of the adult for up to approximately 70 minutes are well below concentrations anticipated to give rise to systemic toxicity. Thus, at recommended dose for single application up to 10 g with application

times of 5-10 minutes to genital mucosa or skin in adults, EMLA® is likely to provide a satisfactory safety margin as regards systemic toxicity.

Two different formulations, the currently marketed formulation and a clinical formulation (carbopol 934, thickening agent was reduced from 1% to 0.4%) were used in the study-83PO26. However, blood concentrations of lidocaine and prilocaine were obtained only from patients who received the currently marketed formulation, therefore, comparisons with respect to concentration levels of lidocaine and prilocaine in (systemic) blood between the two formulations were not made. However, reasonable PK and clinical data is available from the marketed formulation.

PROPOSED PACKAGE INSERT

Note: Strikeouts and underlined text indicate this reviewer's suggested deletions and additions respectively.

81P029: Study on a eutectic EMLA cream used as anaesthetic agent for cervical curettage and vacuum abortions (802-10 AC017-2).

Reference: Volume 2
Investigators: Birgit Kull, M.D.
Study Location: S-791 82 Falun Sweden (Clinical)
Department of Bioanalytical chemistry, Astra Lakemedel AB. (Analytical)

Objective:

To demonstrate if satisfactory anesthesia for performing cervical curettage or vacuum abortion could be obtained with EMLA cream. The cream was applied both in the vaginal fornices and in the cervical canal.

Formulation: EMLA cream 2% with pH 8.5 or 9.5 – 5 g (50 mg base).

Study Design:

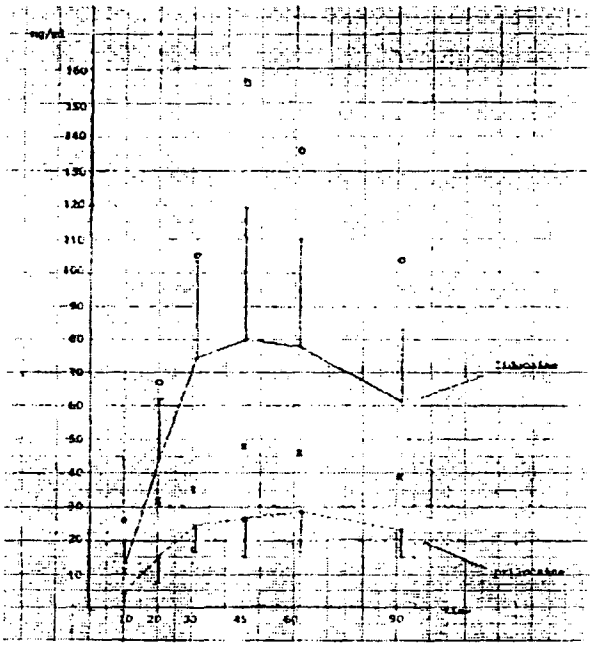
This study was performed in 31 patients who underwent cervical curettage (n = 27) or vacuum abortion (n = 4). The mean age of the group was 32.9 years (range 19-51). The cream (5 ml) was applied in the vaginal fornices and in the cervical canal. Any local discomfort caused by the cream application and analgesic effect during the operation were assessed. Also, blood was collected to obtain levels of lidocaine and prilocaine from the EMLA cream application.

Criteria for Evaluation:
Pharmacokinetic: Individual plasma concentrations.
Clinical assessments: Analgesic effect and patient's acceptance of EMLA.

Analytical Methodology:
Plasma Sampling Times: Prior to and 10, 20, 30, 45, 60, and 90 minutes after cream application (from the first 10 patients).
Assay Method: Mass fragmentography
Assay Sensitivity: The minimum detectable concentration was 10 ng/mL.
Assay Precision/Accuracy: %CV 5%

Results:

The application times in 10 patients ranged from 10 to 20 minutes (mean 14.1 min.). The maximum individual peak concentrations of lidocaine and prilocaine were 156 and 48 ng/ml respectively. Mean peak values were obtained after 46 (ranged from 30-90) and 50 minutes (ranged from 30-90), respectively.



Comments:

- The plasma levels attained from the cream application (for approximately 14 minutes) were much smaller compared to that of reported toxic level.
- Analytical report is not complete (*e.g.*, inter/intra run precision/accuracy, linear range, etc are missing).

Conclusions:

Since this study did not use the marketed strength (5%), this study is not useful in evaluation of this supplement.

83PO26: An Open Study on a 5% Lidocaine-Prilocaine Cream, EMLA, Used as Topical Anesthesia for Cervical Curettage (Report 802-10AC 025-3).

Reference: Volume 2
Investigators: Birgit Kull, M.D.
Study Location: S-791 82 Falun Sweden (Clinical)
Department of Bioanalytical chemistry, Astra Lakemedel AB. (Analytical)

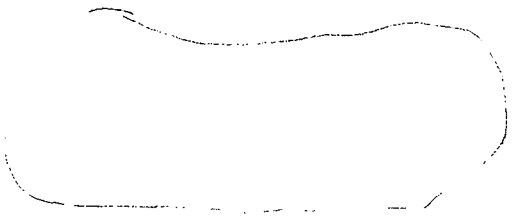
Objective:

To investigate if 10 ml EMLA cream 5% applied in the vaginal fornices would give sufficient analgesia for cervical curettage.

Formulation: EMLA cream 5% with pH 8.5 (12 patients) or 9.5 (27 patients).

pH 8.5

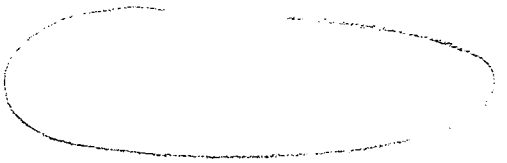
Composition



Marketed Product (composition and pH):

pH 9.5

Composition



Study Design:

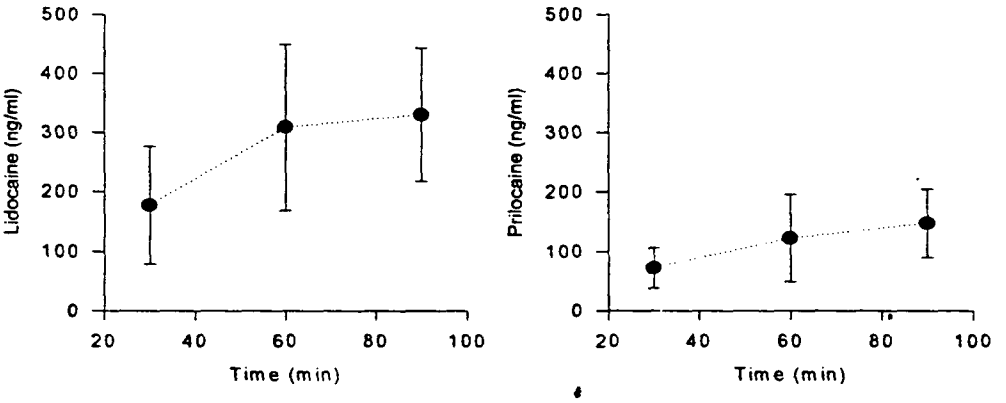
This was an open-label, non-randomized study performed in 39 female patients (aged 18-47 years) with cervical curettage. Before the start of the operating procedure the patient was asked to assess the degree of her uneasiness. After colposcopy, 2 x 5 ml of the cream was applied in the lateral fornices and a cotton swab moistened with saline was applied to keep the cream in the fornices. The application time was 10, 20 or 60 minutes. Towards the end of the application time the patient was asked for any discomfort caused by the cream. The cream was washed away and portio and vagina were inspected for any local adverse reactions. For patients in the 60 minutes group colposcopy was done after removal of the cream. The cervical curettage was then carried out and the patient was asked to assess the pain and discomfort. At a final interview the patient was asked if she would consider EMLA anesthesia in case of a repeated curettage. The investigator made an overall subjective clinical evaluation of the usefulness of the cream after the operation.

Criteria for Evaluation:
Pharmacokinetic: Individual plasma concentrations.
Clinical assessments: Patient's uneasiness before operation, analgesic effect, local reactions, overall clinical assessment and patient's acceptance of EMLA.

Analytical Methodology:
Plasma Sampling Times: 30, 60, and 90 minutes after cream application (pH 9.5; 10 patients) which had 60 minutes application time.
Assay Method: Mass fragmentography
Assay Sensitivity: The minimum detectable concentration was 10 ng/mL.
Assay Precision/Accuracy: %CV 5%

Results:

The mean peak concentrations for lidocaine, 350 ± 141 ng/ml (minimum. 155, maximum 641), and for prilocaine, 158 ± 73 ng/ml (min. 40, max 286) were obtained at 77 ± 16 and 87 ± 10 minutes after start of application, respectively. The highest individual peak concentration for lidocaine was 641 ng/ml and for prilocaine 286 ng/ml was obtained 61 minutes after start of application. The mean (± SD) plasma concentration-time profiles for lidocaine (left) and prilocaine (right) are shown figure below;



Conclusions:

- Venous plasma concentrations of lidocaine and prilocaine were low, however, C_{max} and t_{max} values could be underestimating the true values, judged by the trend of increasing concentrations at the last sampling time (*i.e.*, plasma concentration was the highest at 90 minutes, the last sampling time point).
- Comparison of concentration levels of lidocaine and prilocaine in the blood following a cream with a pH of 8.5 and 9.5 can not be made (different formulation), since blood samples were collected only from patients who received a cream with a pH of 9.5. However, systemic concentration levels of lidocaine and prilocaine following the currently marketed formulation (pH 9.5) are much lower than reported toxic levels.
- No details of analytical methods were provided for review.

83PO36: An open study of EMLA cream, used as topical anaesthetic for prevention of pain during vacuum abortion (Report 802-10AC 024-2).

Reference: Volume 2
Investigators: B. A. Nilsson and K. Holmgren
Study Location: Department of Obstetrics and Gynecology, Stockholm, Sweden (Clinical)
Department of Bioanalytical chemistry, Astra Lakemedel AB. (Analytical)

Objective:

(1) To investigate if EMLA applied only in the vaginal fornices would give sufficient analgesia for vacuum abortion. (2) To assess the plasma levels of lidocaine and prilocaine after vaginal application of 10 ml EMLA 5%. (3) To test a double dummy technique comparing EMLA with paracervical blockade.

Formulation: EMLA cream 5%; 18 and 2 patients received a cream with a pH of 8.5 and 9.5, respectively.

Composition:

Study Design:

This was an open-label, non-randomized study performed in 20 female patients (aged 22-38 years) scheduled for vacuum abortion (the mean gestational age was 8.6 weeks). All patients received premedication (diazepam). Ten milliliter 5% EMLA cream was applied vaginally. Three different methods of application were used; (1) Cream application in fornices in combination with paracervical injections of 0.9% saline. (2) Cream application in the fornices. (3) Cream application both in the fornices and the cervical canal. The application times were 10, 20 and 60 minutes. The patient was instructed to lie on her back during the application period. If the analgesic effect was insufficient (at any stage of the operation), the patient was given general anaesthesia with thiopentone and N_2O/O_2.

Criteria for Evaluation:
Pharmacokinetic: Individual plasma concentrations.
Clinical assessments: Analgesic effect, local reactions, overall clinical assessment.

Analytical Methodology:
Plasma Sampling Times: Before and 10, 20, 30, 45, 60, and 90 minutes after cream application in the group which had 10 minutes application time. In the group with 20 minutes application the last sample was drawn after 120 minutes instead of 90. In the group with 60 minutes application an additional sample was drawn after 180 minutes.
Assay Method: Mass fragmentography
Assay Sensitivity: The minimum detectable concentration was 10 ng/mL.
Assay Precision/Accuracy: %CV 5%.

Results:

The results are summarized in terms of pharmacokinetic parmaeters in the table below following EMLA cream dose.

	Lidocaine		Prilocaine	
Application Site (application time)	C_{max} (ng/ml) Mean ± SD (range)	t_{max} (min) Mean ± SD (range)	C_{max} (ng/ml) Mean ± SD (range)	t_{max} (min) Mean ± SD (range)
Fornix (10 min)	181 ± 32 (148-231)	36 ± 13 (21-60)	148 ± 25 (119-175)	36 ± 13 (21-60)
Fornix (20 min)	201 ± 45 (157-288)	58 ± 31 (30-125)	94 ± 29 (56-133)	43 ± 8 (30-51)
Fornix + Cervix (20 min)	315 ± 169 (158-549)	40 ± 11 (30-53)	178 ± 116 (83-346)	44 ± 10 (30-53)
Fornix + Cervix (60 min)	313 ± 69 (233-355)	97 ± 24 (74-121)	109 ± 34 (87-148)	68 ± 25 (45-95)

Conclusions:

- The highest individual peak concentration for lidocaine was 549 ng/ml, and for prilocaine 346 ng/ml which are about one-tenth of the reported toxic level[1]. This suggests that EMLA applied vaginally with this dosage and application time is well within safe margins.
- No details of analytical methods were provided for review.

[1]Foldes FF, Molloy R, McNall PG, Koukal LR. Comparison of toxicity of intravenously given local anesthetic agents in man. J. A. M. A. 1960; 172: 89/1493-94/1498.

93EML18 (Part II): Human Pharmacokinetics and Bioavailability: EMLA® Cream 5% - Single Use on Genital Skin; A randomized, open label, cross-over study to evaluate the bioavailability of lidocaine and prilocaine from topically applied EMLA cream in males with genital warts.

Reference: Volume 2
Investigators: Birgit Kull, M.D.
Study Location: S-791 82 Falun Sweden (Clinical)
TSI Mason Laboratories, Worcester, MA (Analytical)

Objective:

To determine the bioavailability of lidocaine and prilocaine from EMLA cream used for the relief of pain associated with removal of genital warts.

Formulation: EMLA cream 5% (Lot No, 215-93/1-5); Xylocaine® 1% (Lot No, 310058) and Citanest® Plain (Lot No, 309130).

Actual dose applied (mean ± SD) was 1.0 ± 0.9 g (7.5-82.5 mg base) and 0.7 ± 0.5 g (7.5-55.0 mg base) for lidocaine and prilocaine, respectively. The same patients received 10 mg intravenous reference doses of lidocaine HCl (Xylocaine®) and prilocaine HCl (Citanest®) 7 days later.

Study Design:

The study was of an open label, non-randomized, fixed sequence design in 20 male patients scheduled for removal of genital warts. The absolute bioavailability of lidocaine and prilocaine from topically applied EMLA cream was determined using intravenous administration as reference treatment. Each subject was targeted to receive each of the following treatments as single doses:

EMLA cream 5 g	Dose: 2.5 g cream applied to an area of ≤ 25 cm^2 for 15 minutes. This dose corresponds to 62.5 mg lidocaine and 62.5 mg prilocaine base respectively.
Xylocaine® 1 %	Dose: 10 mg (1 ml, 1% solution of lidocaine hydrochloride) as an intravenous bolus over 1 minute.
Citanest® Plain	Dose : 10 mg (0.25 ml, 4% solution of prilocaine HCl) as an intravenous bolus over 1 minute.

The treatment sequence was EMLA cream first, then Xylocaine®/Citanest® in 7 days later. It was explained to the investigators that they were allowed to apply EMLA cream < 2.5 g depending on the area of application. All areas were occluded with plastic film (Saran Wrap®) for 15 minutes. The actual amount of EMLA administered to each subject was determined by weighing the EMLA tubes before and after administration and the areas of application was measured by a caliper.

Criteria for Evaluation:
Pharmacokinetic: The area under the plasma concentration time curve [AUC_{0-t} and $AUC_{0-\infty}$], maximum plasma concentration [C_{max}], time to maximum plasma concentration [t_{max}], apparent terminal half-life [$t_{½}$], and bioavailability [F].

Analytical Methodology:

Plasma Sampling Times: Prior to application of EMLA cream and 10, 20, 30, 45 minutes and 1, 2, 3, 4, 5 and 6 hours after application, and prior to intravenous lidocaine or prilocaine injections and 1, 2, 4, 6, 8, 10, 15, 30 and 45 minutes and 1, 2, 3, 4 and 5 hours after the end of injection.
Assay Method: GC-MS
Assay Sensitivity: The limit of quantitation was 2.5 ng/mL with linear range of 2.5 to 200 ng/mL
Assay Precision/Accuracy: Intra-run accuracy for lidocaine and prilocaine ranged from -7.9 to 3.2% and -6.5 to 7.4%, respectively. Intra-run precision for lidocaine and prilocaine ranged from ±1.36 to ±3.28% and ±2.11 to ±4.18% over the three runs, respectively. Inter-run precision for lidocaine and prilocaine ranged within ±5.5%.

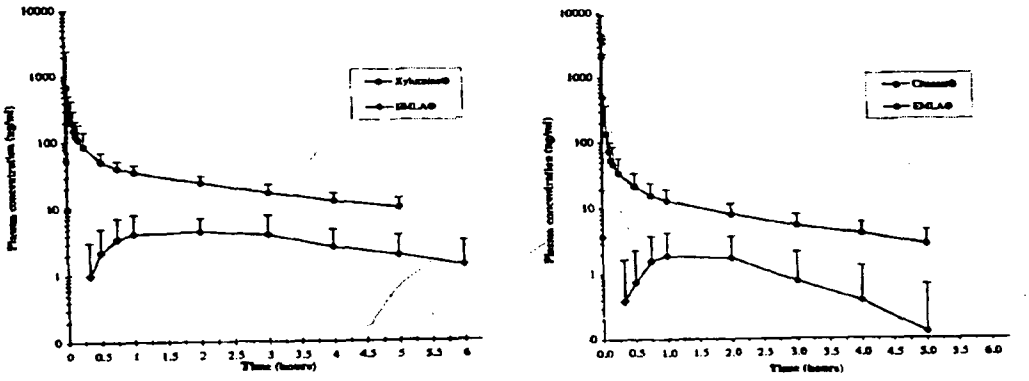
Data analysis: The BA was calculated from the ratio of dose-adjusted values of the $AUC_{0-\infty}$, after topical and intravenous administration.

Results:

The actual mean dose of EMLA was 0.9 g (ranged from 0.2 to 3.3) corresponding to 22 mg (ranged from 5.0 to 82.5) lidocaine and prilocaine base. The results of the pharmacokinetic analysis of lidocaine and prilocaine are summarized in the table, and the mean (± SD) plasma concentration-time profiles for lidocaine (left panel) and for prilocaine (right panel) are shown in the graphs below;

Variable	EMLA Cream (n = 18)	Xylocaine 0 1 % (n = 20)	EMLA Cream (n = 14)	Citanest Plain (n = 18)
AUC_{0-t} (ng/ml • h)	19.1 ± 11.9	163.4 ± 95	5.5 ± 5.7	109.8 ± 180.2
$AUC_{0-\infty}$ (ng/ml • h)	32.4 ± 14.5	196.6 ± 108	12.9 ± 5.4[b]	119.8 ± 180.5
C_{max} (ng/ml)	6.6 ± 3.8	714 ± 1713	4.1 ± 1.5	2401 ± 7648
T_{max} (h)	1.59 ± 0.78	0.05 ± 0.05	1.35 ± 0.83	0.06 ± 0.05
F_{AUC0-t} (%)	9.3 ± 7.9	100	2.2 ± 2.3	100
$F_{AUC0-\infty}$ (%)	13.8 ± 11.6	100	6.0 ± 3.2	100
$t_{1/2}$ (h)	3.5 ± 1.1[a]	2.2 ± 0.5	NA[c]	2.0 ± 0.2

[a] n = 12 [b] n = 12
[c] Not assessed due to insufficient data to estimate individual terminal slopes



Conclusions:

- Plasma concentrations of both lidocaine and prilocaine were low following EMLA application.
- The mean systemic bioavailability of lidocaine (n=18) was 14 % (individual range 1.8 to 38.8 %) whereas prilocaine bioavailability (n= 12) was 6 % (individual range 3.4 % to 14.0%) when applied to genital skin.
- The sponsor stated that plasma concentrations of lidocaine and prilocaine were extremely high following iv administration of these drugs in two subjects: C_{max} for prilocaine was 8218 and 32076 ng/ml in these two patients, with no experience of any adverse events. If the above subjects are excluded from the analysis, the mean bioavailability changes from 13.8 % (n= 18) to 14.2 % (n= 16) for lidocaine and from 6.0 % (n= 12) to 6.5 % (n= 10) for prilocaine. On the other hand per the sponsor, two subjects had no measurable (< ELOQ) plasma concentrations of prilocaine after the intravenous administration and thus resulting in no BA estimate in these two subjects. However, their plasma concentrations of prilocaine after administration of EMLA cream were similar to those observed for the other subjects.
- In general, the precision of BA estimates was large (e.g., CV for AUC and C_{max} were 164 and 319%, respectively, and plasma concentrations of prilocaine in 2 subjects was not detectable following prilocaine iv injection). In addition, the poor parameter estimates are likely to carry over to values of related variabilities.
- BA estimation would have been more desirable with the data following an application from the intended site, mucous membrane than that from the skin.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: January 28, 2000

TO: File, NDA 19-941

FROM: Bob A. Rappaport, M.D. 1/28/00
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

RE: SE1-011: DSI Inspections

No DSI inspections were requested for or performed on the clinical trials in this efficacy supplement for EMLA. The trials in the submission were designed to test the safety and effectiveness of EMLA Cream for the same indications for which the product had been previously approved, with minor changes, i.e., topical anesthesia for minor, superficial surgical procedures or for injection of local anesthetic drugs. The only change in the new indications was in the type of integument to be anesthetized. This supplement extends the use of EMLA for topical anesthesia from the skin to the female genital mucosa. As it was thought to be exceedingly unlikely that EMLA Cream would not be effective in this setting, and the primary concern of the medical review team was the potential for new safety concerns, no inspections were requested.

Thomas McCormick MD
1-28-2000

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Reviewer: M. Anwar Goheer
Division: Division of Anesthetic, Critical Care and Addiction Drug Products.
HFD: 170
NDA: 19-941 Supplement No. 11
Submission: NDA Supplement Dated: March 29, 1999
Received by Reviewer: April 5, 1999
Review Completed: Nov. 1, 1999
Sponsor: AstraZeneca LP. (Previously Astra Pharmaceuticals, LP.),
725 Chesterbrook Boulevard, Wayne, PA 19087-5677
Information to be conveyed to the sponsor: Yes
Drug Name: EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%)
Chemical Name: Lidocaine: acetamide, 2-(diethylamino)-N- (2,6-dimethylphenyl).
Prilocaine: propanamide, N- (2-methylphenyl)-2-(propylamino)
Proprietary Name: EMLA Cream
Compositions: Each gram of EMLA contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), carboxypolymethylene (as a thickening agent), sodium hydroxide to adjust a pH approximating 9, and purified water to 1 gram.
Pharmacologic Class: Local anesthetic
Indication: Dermal analgesic for topical use on intact skin and on genital mucous membranes
Route of Administration: Epicutaneous
Dosage Form: Cream
Clinical Use: This supplement adds the following indication for Adult Patients-Genital Mucous Membranes: For minor procedures involving the cervix, such as cervical curettage and cervical biopsy, apply 5 grams of EMLA Cream in each of the lateral vaginal fornices for 10 minutes. For minor surgical procedures on the external genitals, such as removal of condylomata acuminata and vulval biopsies, as well as for use as an adjunct prior to local anesthetic infiltration, apply a thick layer (5 to 10 grams) of EMLA Cream for 5 to 10 minutes.

Studies Reviewed Within This Submission:

A. Toxicology

(1) Local Toxicity of EMLA in Female Dogs After Single Administration into the Uterine Cavity via Laparotomy. Volume 1/ page 46.
(2) Vaginal Irritation in Dogs After Topical Administration of Xylocain®/Citanest® (EMLA) on 20 Consecutive Days. Volume 1/ page 80.
(3) General Toxicity of EMLA Given Rectally to Dogs for One Month. Volume1/ page 129.

B. Pharmacokinetic

(1) Evaluation of Plasma Concentrations of Lidocaine and Prilocaine in the Study. General Toxicity of EMLA Given Rectally to Dogs for One Month. Volume 1/ page 324.

Studies not Reviewed within This Submission: None

Note - Portions of this review were excerpted directly from the sponsor's submission.

Toxicology

(1) Local Toxicity of EMLA in Female Dogs After Single Administration into the Uterine Cavity via Laparotomy.

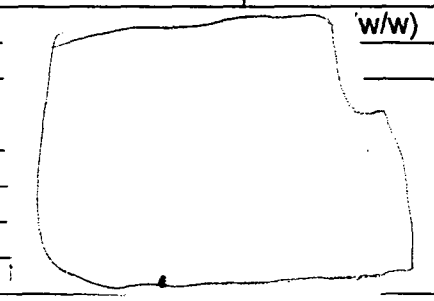
Study No.: 83019 Project No.: 802-10
Study Site: AB Astra, Toxicology Laboratories, S-151 85 Sodertalje, Sweden.
Date: Jan. 2, 1999
GLP/QA Statements: Yes
Test Compounds:

Generic name	Lidocaine base	Prilocaine
Molar mass (g)	234.3	220.3
Batch number	1621P	F 11
Assay (%)	99.8	99.5

Source: Astra Lakemedel AB, Sweden.

The compositions of EMLA and placebo creams

	Placebo cream	EMLA 2% cream
Lidocaine base		w/w)
Prilocaine		
Arlatone 289		
Carbopol 934		
Sodium hydroxide p.a.		
Purified water		
pH		
Batch number		



Animals:

Species: Dog Strain: Beagle
Number and sex: 6 females Age: 12-20 months
Body weight: 8.0-10.2 kg.

Dose groups:

Group No.	No and sex	Animal no.	Compound	Dose (ml)
1	2F	165/83, 166/83	Phys. Saline	0.3 x 2*
2	2F	167/83, 168/83	EMLA placebo	0.3 x 2*
3	2F	169/83, 170/83	EMLA 2%	0.3 x 2*

* 0.3 ml is placed in each cornu, total dose 6 mg EMLA/cornu.

Surgical and administration procedures:
Each dog was treated with subcutaneous medroxyprogesterone to ensure that they were in anestrus phase during the study. Surgical procedure was performed under anesthesia. Uterine centesis was performed in the center of each suture, and the test article was placed in the lumen. Wound closure was performed in two layers using Dexon 2-0. All animals were sacrificed and autopsied 3 days after treatment.

Results:

Clinical observation: No clinical signs of toxicity were observed.
Food consumption, body weight and rectal temperature: Normal
Pathology: Tissue samples from ovaries, oviducts, both uterine horns, uterine body and the uterine cervix were examined microscopically.

Group No.	Dog No.	Phase of estrus cycle	Uterine cervix including vaginal fornix	Uterine body	Uterine horns	Oviducts	Ovaries
1	165/83	Proestrus	-	-	1	-	-
1	166/83	Anestrus	-	-	-	-	-
2	167/83	Metestrus	-	-	-	-	-
2	168/83	Metestrus	-	-	2	-	-
3	169/83	Metestrus	-	-	2	-	-
3	170/83	Proestrus	-	-	-	-	

- = No changes
1 = A small area of sloughed-off endometrium, fibrin exsudation and inflammatory cell reaction in the endo- and myometrium of the right uterine horn.
2 = Focus of slightly increased leukocyte infiltration in the left uterine horn.

Half the animals from each group showed the changes in uterine horns. No significant compound related local irritation was observed.

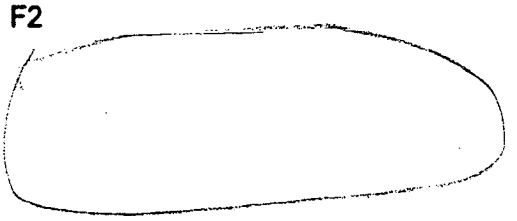
(2) Vaginal Irritation in Dogs After Topical Administration of Xylocain®/Citanest® (EMLA) on 20 Consecutive Days.

Test substance:	Name	Xylocaine®	Citanest®
	Molar mass	234.3	220.3
	Batch No.	1554	01/78
	Purity	99.4%	99.6%
	Source	Astra	Astra

Placebo cream for EMLA 5.0% cream:

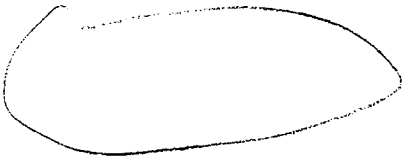
Batch No. F2

Composition

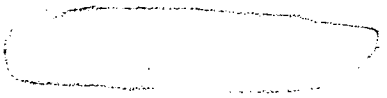


EMLA 5.0% cream:

Batch No. F13



Xylocaine® or Citanest®Injection Solution



Animals: Female Beagle dogs, 7-11 months old,

Supplier: Kennel Rahojden, Orkelljunga, Sweden.

Dose groups:

Group No.	No. of animals	Animal ref. No.	Treatment
1	6	1/80 –6/80	Placebo cream, vaginally, 1 ml
2	6	7/80-12/80	EMLA 5.0% cream, vaginally, 1 ml
3	2	27/80-28/80	Xylocaine/Citanest 50 mg, intravenously

Procedure: All dogs received a single subcutaneous injection of 1.8 ml Gestapuran to synchronize their estrus cycles four weeks before the start of dosing. Approximately 1 ml of the relevant cream was applied into the vagina daily for 20 days. The animals were examined 1 and 24 hours after the administration of the creams for signs of vaginal irritation. Vaginal microbiological samples were taken on days 0, 9 and 19 of the administration. Body weight, rectal temperature, food consumption, clinical signs and examination of the vaginal microbiological flora were performed. Blood samples were also taken before and after (10, 20, 30, 45, 60, and 90 minutes) administration of the drug. Specimens of cervix including portio and fornix vaginae, and vagina 2 cm inside the introitus vagina were taken for histopathological examination.

Vaginal irritation grading (scoring): The grade of reaction was judged according to Draize -FHSA scoring system as given below.

No erythema (pale or pink) 0

Slightly increased erythema (slightly red)	1
Definitely increased erythema (red)	2
Marked erythema (very red) and/or petechial and point bleedings	3
Severe erythema (beetroot red) with bleeding	4

Study dates: Jan. 23, 1980 to Feb. 12, 1980
GLP/QA Statements: Yes

Results:

Body weight, rectal temperature, and food consumption were normal throughout the trial.
Clinical signs: Dogs 9/80 and 12/80 (group 2) have exudation (occasionally blood mixed) on different days.
Vaginal reaction (scoring):

Mean 20 day values for vaginal observations in the control or test group after daily application of placebo or 5.0 % EMLA cream

Observation	Placebo	EMLA	Tail probability (comparison placebo/EMLA)
Zero values (before start of trial)	0.833	0.528	40.1 %
1 hour after application of formulations	1.150	1.308	68.8 %
24 hours after application of formulations	0.783	1.275	14.1 %
Difference between 1 hour and zero readings	+ 0.317	+ 0.781	8.6 %
Difference between 24 hour and zero readings	- 0.050	+ 0.747	0.3 %*
Difference between 24 and 1 hour readings	- 0.367	- 0.033	6.8 %

* significant $P < 0.01$

Mild irritations were observed both in placebo and 5% EMLA cream groups at 1 hour after application. At 24 hour after application of the test formulations, the placebo group showed

recovery but the EMLA group did not show any regression of erythema. The mean 20-day reaction values of the two groups were equivalent.

Microbiological sampling:

Dog #	Finding
1/80, 2/80, 3/80 and 4/80 (control group)	Occasional to moderate growth on all samples.
6/80 (control group)	Zero sample: plentiful growth 9 and 19 day samples: occasional growth
7/80 and 10/80 (treated group)	No or occasional growth in zero samples. And plentiful growth in 9 and 19 day samples
8/80 (treated group)	Zero sample: moderate growth 9 and 19 day samples: plentiful growth
5/80 (control), 9/80 (treated), 11/80 (treated) and 12/80 (treated group)	Plentiful growth on all samples.

The bacterial growth in 5% EMLA cream treated group slightly increased over the control group, but probably represented normal variation. Treatment with placebo or EMLA cream for 20 days did not influence the bacterial flora of the experimental animals.

Plasma Concentration and Pharmacokinetic:

Plasma concentration (Mean±S.D)

Time (min)	After first dosing		After last dosing	
	Lidocaine (ng/ml)	Prilocaine (ng/ml)	Lidocaine (ng/ml)	Prilocaine (ng/ml)
0			<10	<10
10	354±99	164±47	371±138	179±54
20	395±104	187±48	422±144	202±65
30	348±120	170±52	422±136	209±71
45	306±148	136±57	414±165	193±63
60	235±142	108±50	376±161	171±61
90	111±75	54±26	224±96	102±46

Maximum plasma concentrations of both lidocaine (320-565 ng/ml, 448±87 ng/ml) and prilocaine (155-260 ng/ml, 205±37 ng/ml) were reached 10-45 minutes after single administration of EMLA.

Area under the plasma concentration versus time curves (AUC $ng.ml^{-1}.min.10^{-3}$) of lidocaine and prilocaine:

Dog no.	Lidocaine		Prilocaine	
	$AUC_{day\ 1}$	$AUC_{day\ 19}$	$AUC_{day\ 1}$	$AUC_{day\ 19}$
7/80	16.14	31.30	8.52	16.31
8/80	13.97	16.12	6.78	7.82

Dog no.	Lidocaine		Prilocaine	
	$AUC_{day\ 1}$	$AUC_{day\ 19}$	$AUC_{day\ 1}$	$AUC_{day\ 19}$
9/80	29.42	26.74	11.80	13.16
10/80	28.00	25.88	12.63	13.04
11/80	32.72	44.02	14.50	20.83
12/80	20.10	43.31	11.26	17.16
Mean±S.D.	23.39± 7.70	31.22± 10.83	10.92± 2.81	14.72± 4.44

AUC_{day19} /$AUC_{day\ 1}$ ratio for lidocaine and prilocaine:

Dog no.	$AUC_{day\ 19}$/$AUC_{day\ 1}$	
	Lidocaine	Prilocaine
7/80	1.94	1.92
8/80	1.15	1.15
9/80	0.91	1.11
10/80	0.92	1.03
11/80	1.35	1.44
12/80	2.16	1.52
Mean ± S.D.	1.41±0.53	1.36±0.33

This apparent 40% increase in $AUC_{day\ 19}$/$AUC_{day\ 1}$ is not supported by the data. (1). There is a large variation in AUC values (13.97 – 32.72 and 6.78 – 14.50 $ng.ml^{-1}.min.10^{-3}$for lidocaine and prilocaine on day 1, respectively) as shown above. (2). The C_{max} and t_{max} of both lidocaine and prilocaine did not change significantly after 20 days of dosing. (3). The half-life of lidocaine in dog is 1-2 hours [J Vet Pharmacol Ther 1981; 4(2): 129-33]. (4). Blood samplings were done for 90 minutes only. (5). Small number of animals was used. (6). Rectal administration of EMLA cream in dogs did not show any increase in $AUC_{day\ 21}$/AUC_{day1} of both lidocaine and prilocaine (see next experiment).

Systemic availability (F=AUC_{vag} /mean AUC_{IV}) of lidocaine and prilocaine:

Dog no	Lidocaine		Prilocaine	
	AUC($ng.ml^{-1}.min.10^{-3}$)	F	AUC ($ng.ml^{-1}.min.10^{-3}$)	F
27/80	39.31	1.00 (I.V.)	17.38	1.00 (I.V.)
28/80	45.15	1.00 (I.V.)	16.35	1.00 (I.V.)
7/80	16.14	0.38	8.52	0.50
8/80	13.97	0.33	6.78	0.40
9/80	29.42	0.70	11.80	0.70
10/80	28.00	0.66	12.63	0.75
11/80	32.72	0.77	14.50	0.86
12/80	20.10	0.48	11.26	0.67
Mean±S.D.	23.39±7.70	0.55±0.18	10.92±2.81	0.65±0.17

The estimated systemic availability was 55% (range 33-77%) for lidocaine and 65% (range 40-86%) for prilocaine. These data suggest a by-pass of the liver following vaginal administration.

Pathology:

Pathology	Group 1. Placebo						Group 2. Xylocain®/Citanest® 5 % cream					
	Dog No.						Dog No.					
	1/80	2/80	3/80	4/80	5/80	6/80	7/80	8/80	9/80	10/80	11/80	12/80
Gross changes	.	.	.	.	7	.	.	.	.	8	9	
Microscopic changes												
Portio	1	.	.	1	.	1	.	.	.	1	1	10
Fornix	1	.	1	1	1	1	1	.	.	1	1	10
Vagina	2	.	4	2	.	5	4	6	4	4	6	6
Estrous cycle stage	3	3	3	3	3	3	3	3	3	3	3	3

. = No changes

1 = Focal slight lymphocyte infiltration in the mucosa

2 = Moderate degree of chronic colpitis

3 = Diestrus

4 = Slight degree of chronic colpitis

5 = Moderate degree of chronic colpitis with patchy epithelial hyperplasia

6 = Slight degree of chronic colpitis with patchy epithelial hyperplasia

7 = Slight cyanosis

8 = A few brown petechiae on the mucosal foldings

9 = Sparse amounts of yellow mucus

10 = Diffuse infiltration of mainly lymphocytic cells in the mucous membrane

The treatment did not have any apparent adverse effect at the application sites or hormonal effects on the vaginal epithelium. Slight to moderate degree of chronic colpitis was observed in both groups. The possibility of a relationship between treatment and the endometritis-endocervicitis in dog 12/80 (5% EMLA group) can not be ruled out.

(3) General Toxicity of EMLA Given Rectally to Dogs for One Month.

Test compounds:

Lidocaine base: Batch # 1621 [redacted] used for the 2% EMLA cream
Batch # 28530-02, [redacted] purity, used for the 5% EMLA cream
Prilocaine: Batch # F 12 B, [redacted] ty, used for the 2% EMLA cream.
Batch # F 11, [redacted] used for the 5% EMLA cream
Supplier for both drugs: Astra Lakemedel AB, Sweden.
Formulations:

Compound (%)	Placebo (formulation 1)	EMLA 2% cream (formulation 2)	EMLA 5% cream (formulation 3)

Animals: Species – dog Strain – Beagle Age – 8-9.5 months Body weight - males: 8.4-14.8 kg and females: 7.2-13.3 kg
Dosing dates: 26-27 April 1983 to 24-26 May 1983.
Route: Rectal
Clinical signs (daily), food consumption (daily), body weight (weekly), and rectal temperature (weekly) were measured during the study. A proctoscopical examination was performed before the start of dosing. Special attention was directed during the first hour after dosing to see if defecation occurred and if the feces contained formulation.
ECG recording were done before dosing and 1, 3, and 24 hours after dosing on experimental days 0 and either Day 21 or Day 23. In groups 1 and 5 the amplitudes of P, Q, R and S wave, S-T-J, S-T segment and T waves, and the P-R, QRS and Q-T intervals were measured in all the leads. Heart rate was determined by counting the number of R waves within a 15-second time interval.
Ophthalmoscopy: Before and the end of the study.

Dose groups and animal numbers

Group no.	No. and sex	Animal reference number	Compound	Daily dose LMLA mg/kg	Administration volume cream ml/kg	Formulation
1	3 M 3 F	429/83-431/83 432/83-434/83[1]	Untreated	-	-	-
2	3 M 3 F	435/83-437/83[2] 438/83-440/83	Placebo	-	0.25	1
3	3 M 3 F	441/83-443/83 444/83-446/83	EMLA 2%	5	0.25	2
4	3 M 3 F	447/83-449/83 450/83-452/83	EMLA 2%	12	0.60	2
5	3 M 3 F	453/83-455/83 456/83-458/83	EMLA 5%	12.5	0.25	3

Group 1 was not treated with a test or placebo formulation, but in all other respects it was identical to the other groups.

[1]Dogs 432/83, 433/83 and 434/83 accidentally received EMLA 2% on day 13. However, the dogs were immediately purged with 100 ml physiological saline, and the correct dose of placebo was given.

[2]Dogs 435/83, 436/83 and 437/83 accidentally received 0.60 ml/kg of EMLA placebo on day 0

Clinical pathology: The following parameters were analyzed.

Hematology

Packed cell volume (PVC)
Hemoglobin (HB)
Erythrocytes (RBC)
Sedimentation rate (SR)
Reticulocytes (RTC)
Erythrocyte indicies (MCV, MCH, MCHC)
Leukocytes (WBC)

Differential leukocyte counts (BAND, SEG, EOS, BASO, LYMF, MONO, IMM)
Platelet counts (TRC)
Activated Partial thromboplastin time (APTT)

Blood chemistry

Glucose (GLS)
Bilirubins (BLR)
Urea (URE)
Total serum protein (TSP)
Albumin (ALB)
Quotient albumin/globulin (A/G)
Cholesterol (CHL)
Alkaline phosphatase (AP)
Aspartate aminotransferase (ASAT)
Alanine aminotransferase (ALAT)
Ornithine carbamoyltransferase (OCT)
Sodium (SNA)
Potassium (S-K)
Calcium (SCA)
Chloride (SCL)
Magnesium (SMG)
Phosphate (S-P)

Urinalysis

pH (U-PH)
Osmolality (UOSM)
Protein (UPTN)
Glucose (UGLS)
Keto-bodies (UKET)
Occult blood (UOCC)
Bilirubins (UBLR)
Analysis of sediment:
- Red blood cells (URBC)
- White blood cells (UWBC)
- Epithelial cells (UEPT)
- Casts (UCST)

Pathology: Tissue samples for microscopic examinations were taken from the following organs.

Brain	Liver	Adrenal gland
Optic nerve	Gallbladder	Kidney
Sciatic nerve	Pancreas	Urinary bladder
Eye	Heart	Testis
Trachea	Aorta	Epididymis
Lung	Bone marrow	Prostate
Tongue	Cervical lymph node	Ovary
Submandibular gland	Mesenteric lymph node	Fallopian tube
Esophagus	Spleen	Uterus
Stomach	Thymus	Vagina
Duodenum	Pituitary gland	Female mammary gland
Jejunum	Thyroid and	Skin
Ileum	Parathyroid glands	Skeletal muscle
Colon		
Rectum and anus		

The specimens were stained with hematoxylin and eosin. The rectum and anus specimens were additionally stained with a combination of alciane blue pH 2.5 and periodic acid Schiff (PAS) stain.

Plasma concentration: Blood samples were taken before dosing and 30 min., 1, 3, and 24 hours after dosing on days 0 and 21 or 23 from jugular vein.

Statistical analysis: No statistical analysis was performed due to small number of animals.

GLP/QA Statements: Yes

Results:

Clinical signs: Defecation within one hour after dosing in most of the animals. No significant drug product was present in the feces. Rectal bleeding was observed in the following animals.

Dog number	Group	Sex	Day
434/83	1	F	19
443/83	3	M	4
451/83	4	F	5 & 25

Food consumption: Normal
Body weight: No significant change.
Rectal temperature: Normal
Electrocardiography: No significant changes occurred during the study.
Ophthalmoscopy: No effect related to treatment could be detected.
Clinical pathology:
Hematology, blood chemistry and urinalysis: No effect.
Gross pathology: No significant findings.
Organ weights: No significant differences
Microscopic pathology: Number of animals per group per sex (total 3 M & 3 F/group) displaying histopathological changes is shown below.

Summary of microscopic finding

Organ		Group 1		Group 2		Group 3		Group 4		Group 5	
		M	F	M	F	M	F	M	F	M	F
Lungs (lympho-histiocytic granulomis)		1	1	-	2-	-	2	0	1-	1	1
Jejunum (ascarid worms)		-	-	-	-	-	-	-	1	1	-
Rectum and anus	Dermatitis	-	1	-	1	-	-	-	-	-	-
	Hyperemic mucosa	-	1	-	-	-	-	-	-	-	-
	Perifolliculitis	-	-	-	-	-	-	-	-	-	1
Liver (microfocal necrosis)		1	-	1	-	1	1	-	-	1	-
Thymus (slight involution		1	1	1	-	1-	2	1	1	1	1
Pituitary gland (microcyst)		-	1	1	1	-	1	-	1	1-	-

Organ	Group 1 M	Group 1 F	Group 2 M	Group 2 F	Group 3 M	Group 3 F	Group 4 M	Group 4 F	Group 5 M	Group 5 F
Thyroid gland (C-cell hyperplasia)	1	2	-	2	-	2	2	-	2	-
Adrenal gland (cortical nodulus)	-	1	1	-	-	-	-	-	-	1
Kidney (lympho-histiocytic granuloma)	-	2-	-	2	1	1	-	1	1	-
Urinary bladder (focal cystitis)	-	1	1	1	-	1	-	1	-	1
Prostate (microfocal prostatitis)	1	-	1	-	3	-	1	-	1	-
Ovary (large, occasionally cystic corpora lutes)		2	-	-	-	1	-	2	-	2

There were no significant histopathological findings that could be related to test compound. Microscopic examination of rectum and anus (dermatitis, hyperemic mucosa and perifolliculitis) did not reveal any EMLA cream treated adverse effects.

(4) Evaluation of Plasma Concentrations of Lidocaine and Prilocaine in the Study. General Toxicity of EMLA Given Rectally to Dogs for One Month.

Formulations:

Compound (%)	Placebo (formulation 1)	EMLA 2% cream (formulation 2)	EMLA 5% cream (formulation 3)
[redacted]			

Animals: Species – dog Strain – Beagle
Body weight - Male: 8.4-14.8 kg and females: 7.2-13.3 kg
Age – 8 - 9.5 months 3 animals/sex/group (same as experiment #3)

Route: Rectal
Dosing: Daily
Dose groups: (1) untreated, (2) EMLA placebo cream, (3) 5.0 mg/kg (2% EMLA), (4) 12 mg/kg (2% EMLA cream) and (5) 12.5 mg/kg (5% EMLA)
Blood samples were taking from jugular vein on days 0 and 23, before dosing and at 0.5, 1.0, 3.0 and 24 hours after dosing.
Study dates: Experiment was conducted during April to May 1983. Bioanalysis was performed in October-November 1983
GLP/QA Statements: Yes

Results:

Plasma Concentration (ng/ml) [Mean±S.D]

Group #		Plasma concentration of lidocaine (ng/ml) on day 0 at				
		h,	0.5 h	1 h,	3 h	24 h
1	M	<10	<10	<10	<10	<10
	F	<10	<10	<10	<10	<10
2	M	<10	<10	<10	<10	<10
	F	<10	<10	<10	<10	<10
3	M	<10	97±77	143±92.0	<10	<10
	F	-	244±321	214±321	<10-30	<10-
4	M	<10	185±77	234±49	145±53	<10
	F	<10	92±23	160±13	72±33	<10
5	M	<10	124±26	170±63	119±76	<10
	F	<10	114±30	109±61	65±29	<10

Group #		Plasma concentration of lidocaine (ng/ml) on day 21-23 at				
		0.0 h,	0.5 h	1 h,	3 h	24 h
1	M	<10	<10	<10	<10	<10
	F	<10	<10	<10	<10	<10
2	M	<10	<10	<10	<10	<10
	F	<10	<10	<10	<10	<10
3	M	<10	85±45	84±30	19±4	<10
	F	-	135±99	199±73	34±8	
4	M	<10	99±7	116±11	78±48	<10
	F	<10	145±60	115±24	96±43	<10
5	M	<10	133±99	142±84	99±83	<10
	F	<10	156±26	79±36	26±5	<10

AUC $_{0\text{-}3h}$ (ng.h/ml) [Mean±S.D.]

Group	Sex	Day 0		Day 21-23	
		Lidocaine	Prilocaine	Lidocaine	Prilocaine
3	M	239±153	-	169±62	41±6
	F	409±515	202±226	346±149	110±108
4	M	532±69	141±46	275±63	73±5
	F	320±34	100±23	316±100	92±33
5	M	396±110	130±49	346±157	117±38
	F	260±100	112±29	206±61	84±24

Cmax (ng/ml) [Mean±S.D.]

Group	Sex	Day 0		Day 21-23	
		Lidocaine	Prilocaine	Lidocaine	Prilocaine
3	M	143±92	-	91±35	18±3
	F	244±321	122±124	199±73	97±57
4	M	248±39	75±24	119±15	30±1
	F	160±13	50±13	150±52	44±17
5	M	186±65	69±33	168±92	55±23
	F	138±43	53±8	156±26	55±12

The absorption of both drugs was similar with a t_{max} between 0.5 – 1 hour on both days 0 and 23. There were no significant differences in C_{max} on days 0 and 23 indicating no cumulative effects. Due to large variation in individual values and small number of animals, the AUC values were highly variable (164 to 436 ng.h.ml^{-1} of lidocaine in males and 161 to 275 ng.h.ml^{-1} of lidocaine in females of group 5 on day 21) of both drugs. Lidocaine and prilocaine could not be detected in the plasma 24 hours after the administration, indicating fast elimination from the blood. There did not appear to have gender effect. The systemic exposure to lidocaine was greater than that of prilocaine on both days 0 and 23.

Overall Summary and Evaluation

EMLA Cream is comprised of lidocaine base (2.5%) and prilocaine base (2.5%). These two different compounds exist as a eutectic mixture in the oil phase of an emulsion. The FDA approved EMLA cream on December 30, 1992 as a topical anesthetic for use on normal intact skin for local analgesia. The package insert also states that "EMLA is not recommended for use on mucous membranes because limited studies show much greater absorption of lidocaine and prilocaine than through intact skin." The purpose of the present supplement NDA is to provide documentation to support safe and effective use of EMLA as a topical anesthetic for superficial minor surgery of genital mucous membranes. Three preclinical toxicity studies and one pharmacokinetic study in dogs submitted in this supplement are summarized below.

Single administration of 12 mg/dog of 2% EMLA cream, placebo cream or saline into the uterine cavity via laparotomy revealed focal reactions in one uterine horn of one dog in each group (total 2 animals/group). This may be due to the administration (surgical) procedure since no other changes that could be related to the treatment with test article were detected. Clinical observation, body weight, food consumption and rectal temperature were within normal limits.

Vaginal irritation after topical administration of 1 ml EMLA cream (5%) daily for 20 days was studied in dogs. The body weight, rectal temperature and food consumption remained normal throughout the experiment. Vaginal microbiological flora on days 0, 9 and 19 did not reveal any

significant infection related to drug application. The mean 20 day irritation values of the placebo and EMLA cream groups were equivalent but a clear significance ($p< 0.01$) was obtained when the difference between the mean zero time and 24 hour reading were compared. This reaction regressed in the placebo group but remained unchanged in the EMLA group after 24 hours of the application. The pathological examination of the genital organs did not show any adverse effects of the test compound at the application site. The systemic availability of lidocaine and prilocaine indicated a by-pass of the liver and reduction of the first-pass hepatic elimination of EMLA cream following vaginal administration. Maximum plasma concentrations of the drugs (320-565 ng/ml for lidocaine and 155-260 ng/ml for prilocaine) were reached within 10-45 minutes after vaginal application. These plasma levels are approximately two fold of the maximum concentration of lidocaine (180 ng/ml) and prilocaine (150 ng/ml) reached in patients after 20 minutes of the application of 10 g of EMLA cream for 10 minutes to vaginal mucosa. These plasma levels in dogs are approximately 10 times below the known human toxic levels for both lidocaine (5000 ng/ml) and prilocaine (6000 ng/ml).

An apparent 40% increase in $AUC_{day\ 19}/AUC_{day\ 1}$ after vaginal administration reported by the sponsor is not supported by the data. (1). There is a large variation in AUC values (13.97 – 32.72 and 6.78 – 14.50 $\mu g.ml^{-1}.min$. for lidocaine and prilocaine, respectively, on day 1) as shown on page 7. (2). The C_{max} and t_{max} of both lidocaine and prilocaine did not change significantly after 20 days of dosing. (3). The half-life of lidocaine in dog is 1-2 hours [J Vet Pharmacol Ther 1981; 4(2): 129-33]. (4). Blood samplings were done for 90 minutes only. (5). Small number of animals was used. (6). Rectal administration of EMLA cream in dogs did not show any increase in $AUC_{day\ 21}/AUC_{day1}$ of both lidocaine and prilocaine. Therefore, data do not support accumulation of drugs after repeated administration of EMLA cream.

One month rectal administration of EMLA cream [2% (12 mg/kg) and 5% (12.5 mg/kg)] in dogs did not indicate any effect on body weight, food consumption, rectal temperature, hematology, and urinalysis. There were no ECG changes or ophthalmic changes associated with treatment. Specifically, there were no histopathological findings in the rectum of 2% EMLA cream or 5% EMLA cream treated groups that could be related to treatment. This study did not show systemic or local toxicity at all the doses tested. No observed adverse effect level (NOAEL) or no observed effect level (NOEL) cannot be determined since lowest observed adverse effect level (LOAEL) could not be established possibly due to small number of animals and/or use of a high dose that failed to produce a clear-cut adverse effect in this study.

The maximum plasma concentrations (C_{max}) of both lidocaine and prilocaine in beagles were reached within 0.5-1 hour after rectal administration. This is similar to that seen in rat, rabbit and man. At the highest dose tested (12.5 mg/kg), the plasma levels of both lidocaine (114-238 ng/ml in males and 89-178 ng/ml in females) and prilocaine (31-88 ng/ml in males and 44-60 ng/ml in females) remained below the human toxic level for these drugs (5-6 $\mu g/ml$). Human safety margin at the highest dose tested in dogs is about 25 times based on TK/PK. The plasma concentrations of prilocaine were lower than that of lidocaine in both male and female dogs. There were no significant differences in either the C_{max} or t_{max} values between the single and repeated administrations. It was not possible to calculate half-life due to insufficient number of data points (2 points) in the terminal phase of elimination. The elimination of both drugs from the blood was fast. No detectable plasma levels (10 ng/ml) of lidocaine and prilocaine were seen 24 hours after the administration in any group.

3 page(s) of revised draft labeling has been redacted from this portion of the review.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B.

[redacted]

/S/

M. Anwar Goheer, Ph.D.

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Concur by Team Leader: Dou Huey (Lucy) Jean, Ph.D.