CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-962

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-962

Trade Name: EMLA Anesthetic Disc

Generic Name:(lidocaine 2.5% and prilocaine 2.5%)

Sponsor:Astra USA, Inc.

Approval Date: February 4, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 20-962

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-962

FEB 4 1998

Astra USA, Inc.
50 Otis Street
Westborough, MA 01581-4500

Attention: Paul J. Damiani, Ph.D.
Associate Director
Regulatory Affairs

Dear Dr. Damiani:

Please refer to your New Drug Application (NDA) dated July 14, 1995, received July 17, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA® Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5%).

We acknowledge receipt of your submissions dated November 21 and December 19, 1996, and November 7, 1997. The User Fee goal date for this application was December 20, 1997.

This new drug application provides for the marketing of EMLA® (lidocaine 2.5% and prilocaine 2.5%) in a new dosage form, a single dose unit of EMLA® contained within an occlusive dressing for use as a topical anesthetic on normal intact skin for local anesthesia.

This application was originally submitted as supplemental application 004 to NDA 19-941. We have reclassified the former supplemental application as an NDA to conform to the "Interim Guidance on Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992". The guidance specifies that, "Different dosage forms should be submitted in separate original applications unless the products are identical (drugs) or alike (biologics) in quantitative and qualitative composition." A copy of the Interim Guidance has been enclosed for your convenience. If you have any questions concerning the Interim Guidance please contact Michael Jones, Program Manager, Center for Drug Evaluation and Research Office of Policy at 301-594-2041.

We have completed the review of this application, including the submitted draft labeling, 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 enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

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 "FINAL PRINTED LABELING" for approved NDA 20-962. Approval of this submission by FDA is not required before the labeling is used.

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

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

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, please contact Ken Nolan, Project Manger, at 301-443-3741.

Sincerely yours,

/S/

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES

cc:
Original NDA 20-962
NDA 19-941
HFD-170/Div. files
HFD-170/CSO/KNolan
HFD-170/MTheodorakis
HFD-170/RKahn
HFD-170/CMcCormick
HFD-170/SDoddapaneni
HFD-002/ORM (with labeling)
HFD-103/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-023/Ann Myers
HFD-005/M.Jones

Drafted by: BCollier/November 24, 1997//Rev./KEN/December 3, 1997/January 15,1998/January 20, 1998/m:n/19941a.d12
Initialed by:
final:

APPROVAL (AP)

ATTACHMENT E
July 12, 1993

INTERIM GUIDANCE

SEPARATE MARKETING APPLICATIONS AND CLINICAL DATA FOR PURPOSES OF ASSESSING USER FEES UNDER THE PRESCRIPTION DRUG USER FEE ACT OF 1992

I. INTRODUCTION

The Prescription Drug User Fee Act of 1992 (User Fee Act) levies a user fee on each "human drug application" including applications: (1) for approval of a new drug submitted under section 505(b)(1) after September 1, 1992; (2) under 505(b)(2) submitted after September 30, 1992 for certain molecular entities or indications for use; (3) for initial certifications or approvals of antibiotic drugs submitted under section 507 after September 1, 1992; and (4) for licensure of certain biological products under section 351 of the Public Health Service Act submitted after September 1, 1992.[1]

The User Fee Act provides for different user fees for original applications depending upon whether they are accompanied by clinical data on safety and efficacy (other than bioavailability or bioequivalence studies).[2] The Act also levies fees on supplements[3] to human drug applications that contain clinical data.[4] Under the fee schedules provided in the User Fee Act, original applications without clinical data, and supplements with

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[1] Section 735(1), 21 U.S.C. § 379g(1).

[2] Section 736(a)(1) and (b), 21 U.S.C. § 379h(a)(1) and (b). Bioavailability/bioequivalence studies are applicable only to applications submitted under sections 505 and 507 of the Federal Food, Drug, and Cosmetic Act. They are not addressed in section 351 of the Public Health Service Act.

[3] Changes to approved biological Product License Applications (PLA's) are called "amendments." Changes to unapproved new drug applications are also called "amendments" but changes to approved new drug applications are called "supplements." For convenience, in this interim guidance, the term "amendment" will be used to refer to changes to NDA's, PLA's, and ELA's submitted before an application is approved and "supplement" will refer to changes to NDA's, PLA's, and ELA's submitted after approval. CBER intends to incorporate this terminology into its regulations.

[4] Section 736(a)(1), 21 U.S.C. § 379h(a)(1).

clinical data, are assessed approximately one-half the fee of original applications with clinical data for fiscal years 1993-1997.

This document provides interim guidance on: (1) what should be contained in separate marketing applications and what should be combined into one application ("bundling guidance") for purposes of assessing user fees; and (2) the definition of "clinical data" for purposes of assessing user fees.

This document is not a proposed rule or a rule.[5] It is not binding on either FDA or sponsors, and does not create or confer any rights, privileges, or benefits for or on any person. It does, however, describe FDA's present intentions regarding what will be considered a separate marketing application and what will constitute clinical data for purposes of the User Fee Act.

A potential applicant should consider this guidance when it prepares its application or supplement. FDA expects to apply this guidance in assessing applications in the foreseeable future to determine whether an application is appropriate for filing. If FDA determines that an application has been inappropriately bundled, or that an applicant incorrectly concluded that an application did not contain clinical data, FDA will notify the applicant and request additional fees, if appropriate. This will not prevent the filing of the application if it is otherwise suitable for filing, or its review, if it is otherwise ready for review. If an applicant disagrees with the determination, it may appeal through appeal procedures to be established later in each Center and, subsequently, to the Ombudsman. Upon completion of the appeal, any fees deemed appropriate will be due and payable.

II. FDA BUNDLING GUIDANCE

In 1975, the Acting Associate Director for New Drug Evaluation issued a memorandum to Bureau of Drugs staff describing when a new NDA should be submitted and when a supplement to an existing NDA should be submitted.[6] This memorandum called for new NDA's for changes in dosage form or major new indications not closely related to an approved indication. The memorandum called for a supplement for a new indication closely related to an approved indication. Other than this internal memorandum, neither the Center for Drug Evaluation and Research (CDER) nor the Center for Biologics Evaluation and Research (CBER) has issued written

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[5] FDA is currently considering proposing a rule governing these issues.

[6] Memorandum from Marion J. Finkel, M.D., Acting Associate Director for New Drug Evaluation to Division Directors and Supervisors, January 9, 1975.

guidance stating which submissions were considered to be one application and which were considered separate applications (NDA or PLA). Similarly, the Centers did not previously specify what should be submitted as a separate original application and what should be submitted as an amendment to a pending application, or as a supplement to an approved original application.

Because different user fees will be assessed on original applications and supplements, FDA believes it is useful to provide guidance to applicants on the agency's interpretation of what constitutes a separate original application, amendment, or supplement.

CDER and CBER interim guidance for determining whether separate applications will be accepted is described below. Section A contains the guidance for original applications and Section B contains guidance on supplements. Nevertheless, the agency may, for administrative reasons (e.g., review across two divisions or offices), assign separate reference numbers and separately track and take regulatory action on the various parts of what is considered to be one application under this guidance document.

A. Original Applications and Amendments[7]

1. Different Active Ingredients Or Combinations of Active Ingredients, or Products

a. Drugs

Every different active ingredient[8] or combination of two or more different active ingredients should be submitted in a separate original application. Products to be marketed as both a racemic mixture and a single enantiomer should be in separate original applications. Similarly, drug substances purified from mixtures with multiple constituents of an active ingredient (e.g., enantiomers, polymorphs) should also be in separate original applications.

b. Biological Products

A biological product is identified in section 351 of the Public Health Service Act (42 U.S.C. § 262), as "any virus,

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[7] "Original application" ordinarily means a complete new filing (NDA, PLA, or ELA) for an applicant. If related but separate applications are submitted, the second and subsequent applications in a series may cross-reference appropriate sections in the initial submission.

[8] Different salts, esters, complexes, etc. of the same active moiety are considered to be different active ingredients.

therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product. . .applicable to the prevention, treatment, or cure of diseases or injuries of man. . ." The Prescription Drug User Fee Act describes those biologicals subject to User Fees.

Individual biological product applications may include a single or combination biological product meeting the above definition which would result in the issuance of a distinct product license. New applications for combination biological products should be submitted when any one of the constituents of the combination is altered in a manner which, for some other reason described in this guidance, warrants a separate application.

2. Different Routes of Administration

Products to be administered using different routes of administration (see Appendix A) should be submitted in separate original applications unless the product(s) for use by all routes in a given application are quantitatively and qualitatively identical (drugs) or alike (biologics) in composition (e.g., an injectable liquid dosage form intended for use by the intravenous and intraperitoneal routes).

3. Different Dosage Forms

Different dosage forms (Appendix B) should be submitted in separate original applications unless the products are identical (drugs) or alike (biologics) in quantitative and qualitative composition (e.g., a sterile liquid in a single dose vial that is intended for use as either an injectable or an inhalation solution).

4. Pharmacy Bulk Packages and Products for Prescription Compounding (CDER)

Pharmacy bulk packages and products for prescription compounding should be submitted as separate original applications and should have their own package insert.

5. Different Strengths/Concentrations

Different strengths or concentrations of one drug substance, active biological product, or combination product, if they are the same dosage form intended for the same route of administration and the same general indication(s) should be submitted in one original application if their qualitative composition is identical (drugs) or alike (biologicals).

6. Excipients

Single entity or combination products with excipients that differ qualitatively or quantitatively to accommodate different container sizes and configurations, or that differ qualitatively or quantitatively with respect to: colors, flavorings, adjustment of pH or osmolality, or preservatives,[9] should be submitted in a single original application unless for some other reason described in this guidance, a separate application is warranted. Differences in excipients that require separate clinical studies of safety or effectiveness should not be included in the same original application. Differences in excipients in topical products that require separate *in vivo* demonstration of bioequivalence should be included in separate original applications.

7. Container Sizes and Configurations

Except for pharmacy bulk packs (see section A.4, above), different container sizes and configurations (e.g., filled syringes, ampules, sealed vials) of one finished pharmaceutical product, intended to be for the same route of administration for the same indication(s) (or otherwise consistent with item 2 and 3 above), should be considered one application for purposes of assessing user fees.

8. Different Indications or Claims

If submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration (or otherwise consistent with items 2 and 3, above) may be regarded, for the purposes of assessing user fees, as one application regardless of:

i. the dose to be administered;

ii. the duration of use;

iii. the schedule of administration;

iv. the population in which the product is indicated; or

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[9] Identical products in both single and multiple dose vials with and without preservatives may be submitted in a single application provided that data are included demonstrating the same clinical activity of the two presentations.

v. the condition for which the product is indicated.

After initial submission, a pending original or supplemental application should not be amended to add a new indication or claim. Previously submitted indications or claims may, however, be modified by, for example, reanalyses of previously submitted data or, in rare instances, supplementary clinical data. Such amendments could result in subsequent adjustments to the user fee review clock. New clinical or *in vitro* data to support a new claim(s) should not be submitted to an already submitted original application during the review of that application. Such a submission would be considered tantamount to developing the product on the review clock and is contrary to the spirit and intent of the User Fee Act. If the original application is not yet approved, a request for approval of other new indications or claims could, however, be submitted in a separate, original application. If the initial application is approved, the application then may be supplemented to add a new indication. See section II.B. on supplemental applications. The basic operating principle should be that, at the time of submission, an original application should be complete and ready for a comprehensive review.

B. NDA Supplements and PLA Amendments

1. Changes in the composition of an approved product to support a change in the dosage form or route of administration (other than those discussed in section I.A.2 or I.A.3 above) should be submitted as a separate original application.

2. Changes to an approved product, based on chemistry, manufacturing or controls data and bioequivalence or other studies (e.g. safety and immunogenicity) that change the strength or concentration, change the manufacturing process, equipment or facility, or change the formulation (e.g. different excipients), should be submitted as supplements to an approved application and do not ordinarily warrant a new original application unless they change the dosage form or route of administration (see items I.A.2 and I.A.3, above).

3. Requests for approval of a new indication, or a modification of a previously approved indication,

should each be submitted individually in a separate supplement to an approved original application.[10]

4. New clinical or *in vitro* data, submitted in support of a new indication or claim other than that required in safety updates, should not be submitted as part of the pending supplement during the review of a given supplemental application. Such a submission would be considered tantamount to developing the product on the review clock and is contrary to the spirit and intent of the User Fee Act. Previously submitted indications or claims may, however, be modified by, for example, reanalyses of previously submitted data or, in rare instances, supplementary clinical data.

5. The basic operating principle should be that, at the time of submission, a supplement should be complete and ready for a comprehensive review. Modifications of the supplement should be only to clarify part of the already submitted supplement or to answer specific questions raised by the review team. Modifications should not be to expand or broaden the scope of the already submitted supplement unless they are requested by the agency.

III. DEFINITION OF CLINICAL DATA

Many different types of applications and supplements may be accompanied by data reporting clinical experiences in humans. Not all such reports of experience in humans are regarded by FDA as "clinical data" for purposes of assessing user fees. For example, FDA does not consider individual case reports describing experience in clinical use submitted in support of a labeling change to add adverse reactions to be "clinical data" under the User Fee Act. Clinical data encompasses a broad range of studies that are purported to be adequate and well-controlled investigations submitted in support of approval.

User fees will be assessed for original applications (NDAs or PLAs) and supplements containing the following types of clinical data required to form the primary basis for approval:

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[10] The Prescription Drug User Fee Act states, "The term "supplement" means a request to the Secretary to approve a change in a human drug application which has been approved." Each indication is considered a separate change for which a separate supplement should be submitted. The policy allows FDA to approve each indication when it is ready for approval rather than delaying approval until the last of a group of indications is ready to be approved.

- study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials; or

- reports of comparative activity (other than bioequivalence and bioavailability studies), immunogenicity, or efficacy, where those reports are necessary to support a claim of comparable clinical effect.

For purposes of assessing user fees, "clinical data" do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication, or warning to the labeling).

Supplements to new drug applications based solely on bioequivalence studies or studies of bioavailability of a drug, are not considered to contain clinical data for purposes of assessing user fees, even if the studies include clinical endpoints.

Supplements to biological product license applications in support of a process or site change which use safety, biochemical equivalence, and/or limited comparative product equivalence data generated in animals or humans as the supportable basis for such a change are not considered to contain clinical data for the purposes of assessing user fees.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-962

MEDICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

NDA # 19-941
Supplemental Application SLR-004

Application for a New Formulation of EMLA® Cream as a Single-Dose Adhesive Disk.

Date of Submission: July 1, 1993 (IND
November 4, 1994 (NDA 19-941)
Received for Review: July 24, 1997
Date of Review: July 29, 1997

Introduction

EMLA Cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%, indicated and labeled for establishing anesthesia of the skin. The mixture of two anesthetics creates an oil emulsion at room temperature which readily absorbs through intact skin. Application of 1-5 gms of EMLA Cream, depending on the clinical indication, under an occlusive dressing, establishes some surface anesthesia in 30-45 minutes, with clinically useful results after application for 60 minutes.

EMLA Cream is indicated for use in a variety of clinical indications when surface anesthesia is desirable, including venipuncture, removal of dermatologic lesions, and harvesting of skin for grafting. The sponsor has developed a unit dose form of EMLA Cream, consisting of a cellulose sponge saturated with 1 gram of the cream, surrounded by an adhesive polyethylene foam ring, with the entire unit adherent to a foil backing. The introduction of a unit dose form of EMLA Cream would be appropriate for one of the most common uses of EMLA Cream, namely anesthesia of the skin prior to venipuncture, while addressing several safety and efficacy issues which may be encountered when EMLA Cream is squeezed from the tube onto the skin surface:

1. Lack of efficacy due to failure to apply an occlusive dressing on top of EMLA Cream.

2. Inadvertent excessive dose due to inability to estimate the correct amount when squeezed from the tube, a potential problem relevant to pediatric use.

3. Possibility of inadvertent contact of cream with eyes

or oral mucous membranes due to contact of cream with the hands during application from the tube.

4. Potential reduction of the risk of toxicity, since the disk contains one gram of EMLA, while the most common dose applied from the tube is one-half of a tube, or 2.5 grams.

Clinical Efficacy and Safety

The bioequivalency of the EMLA unit-dose disk to EMLA Cream under an occlusive dressing was demonstrated by showing equivalent transport of lidocaine and prilocaine across an in vitro preparation of human skin. Detailed review of this study is available in the Biopharmacology review.

The application is supported by four study reports which were submitted in IND and found in Volume 8.5, p. 178 et seq.: Swedish EMLA "patch," and resubmitted with supplement 004, along with a fifth clinical study report in Volume 24.1, p. 75 et seq. of the Development Report.

A summary table of the clinical studies follows.

Investigator, Site, Study #	Objective	Pt. Ages	Numbers of Subjects				Results
			Plan	Enter	Complete	Drop-out	
Vinnars, Sweden, 86-EM-11	Compare analgesic effect of 5% EMLA Cream with Tegaderm dressing to EMLA patch; influence of application time.	years	21	21	21	1: effic	Analgesic effect similar in both groups
Steward, Canada, 89-EM-01	Comparison of single unit package of EMLA to 5% EMLA cream to reduce pain of venipuncture in children	years	175	196	196	0	Analgesic effect similar in both groups

Nilsson, Sweden, 89-EM-04	Comparison of single unit package of EMLA to 5% EMLA cream to reduce pain of venipuncture in children	years	60	63	63	0	Analgesic effect similar in both groups
Goresky, Canada, 62-15	Comparison of single unit package of EMLA to 5% EMLA cream to reduce pain of venipuncture in children	years	36	31	31	4: effic	Analgesic effect similar in both groups
Robieux, Canada, 62-09	Comparison of single unit package of EMLA to 5% EMLA cream to reduce pain of venipuncture in children	years	160	160	160	0	Analgesic effect similar in both groups

Study #1 was an open randomized study comparing a dose of 0.8 gm EMLA per 9.6 cm^2 as a unit dose (patch) or applied from the tube and covered with a Tegaderm dressing. 21 adult volunteers participated. The efficacy data of one subject was excluded because it was recorded incorrectly, but safety data (skin reaction) was recorded in this subject. An additional subject was recruited to replace the efficacy data.

12 doses were applied to each volunteer, 6 to each arm, cream to one and patches to the other. Four application times were studied: 60, 120, 180, and 240 minutes. Anesthesia was tested by pinprick and needle insertion, with reference to an adjacent unanesthetized skin area. Subcutaneous needle insertion pain and pain of venipuncture were assessed using a 100 mm VAS. Skin reactions were also recorded.

Dermal analgesia increased with duration of application, with 120-240 minutes resulting in greater reduction of pain than 60 minutes application.

After 60 minutes application, there was a higher VAS score at the 180 minute pinprick observation time for the cream compared to the patch (9.8 vs 8.4 $p< 0.05$). Otherwise, there were no differences between mean VAS scores for both application methods of EMLA Cream, while both provided significantly reduced VAS scores compared to untreated skin. The local skin reactions were pallor, redness, piloerection over the anesthetic site, and redness over the adhesive site. After 60 minutes of application,

the incidence of skin reactions over the antecubital fossa was higher with cream than with the patch (n=21; 100% vs n=13; 62%, p< 0.01). After 120 minutes of application, the incidence of redness over the adhesive site was significantly higher with the patch than with the Tegaderm dressing (n=11; 52%, vs n=3; 14%, p < 0.01). There were no other efficacy or safety differences.

Study #2 was an open-label, randomized, multicenter study with two parallel groups. Children (parent informed consent) who were undergoing venipuncture for therapeutic reasons received either one EMLA patch or one-half tube of EMLA Cream covered by a Tegaderm dressing applied for 60-180 minutes to the dorsum of the hand or the antecubital fossa. Individuals with allergy or sensitivity to amide local anesthetics were excluded.

Subjects assessed the pain of venipuncture using a three point verbal rating scale (no pain, slight pain, severe pain), and pain due to removal of the adhesive. Observers also assessed reaction to these painful stimuli using the same three point scale. Observers assessed the degree of adhesion of the dressing or patch. The subjects were asked to describe any local sensations during the application period, especially itching or burning. Observers assessed local skin reactions after the patch or dressing was removed.

One-sided 95% confidence interval for the difference between the two groups < 0.2 regarding the proportion of no or slight pain was judged to entail no clinically significant difference. Power calculation of 90% for equal proportions at 0.9 required 80 patients per group. 178 patients were valid for "per protocol" efficacy analysis; all patients were valid for "all patients treated" analysis of efficacy and safety.

Per protocol analysis and all-patients-treated analysis of efficacy gave the same results. 95% in the EMLA patch group and 94% in the EMLA Cream group reported no or slight pain from venipuncture. The lowest limit for the two 95% confidence intervals was 0.89 and the highest limit was 0.99 (difference 0.11). No or slight pain as assessed by the investigator was 95% in the EMLA patch group and 97% in the EMLA Cream group. The difference between the two confidence intervals was 0.11. Adhesion was superior for the Tegaderm dressing compared to the patch: > 75% adhesion 80% for the patch vs 92% for Tegaderm, p < 0.001. There was no significant difference in the ratings of discomfort associated with removal of the adhesive dressing, reported as none or slight in all but one patient. Pallor under the adhesive was seen in 5 patients in the EMLA patch group and in no patients in the cream group. There were no other differences in local skin reactions (pallor, redness, edema) between the two groups. Mild burning at the skin site during application was reported by one patient (patch); itching was reported by 18 patients in the patch group and 13 patients in the cream group (p= NS). The study concluded that there were no

efficacy or safety differences between the two treatment groups.

Study #3 was an open-label randomized study at a single institution. 63 children between the ages of 5-15 who were scheduled for inpatient or outpatient surgery received either 5% EMLA Cream, 2.5 gm, covered by a Tegaderm bandage or the unit dose EMLA patch on the dorsum of the hand for 60-180 minutes prior to venipuncture for placement of an intravenous catheter. Pain of venipuncture was recorded on a 100 mm VAS scale. The degree of adhesiveness of the two bandages was recorded by the nurse prior to removal. Discomfort associated with removal of the bandage was reported by the child as none, slight, or severe. The child was asked to report local sensations, as per study #2, and the nurse examined the skin for pallor, redness, and edema.

VAS scores were compared by ANOVA with terms for application time, treatment group and application time-treatment group interaction. A one-sided 95% Wilcoxen confidence interval for a VAS difference of < 15 mm was defined as equivalent. Power calculation at 80%, assuming that the true mean VAS scores are equal with a standard deviation of 20 mm, determined that a sample size of 30 per treatment group was required to detect a difference. Two-sided Wilcoxon rank sum test was used to compare adhesiveness, local skin reactions, and discomfort from removal of the patch/Tegaderm.

There was a negative correlation between the VAS score and the application time for both treatments (r= -0.37, p=0.04 and r=-0.38, p=0.04 for patch and cream respectively. Application time had a significant effect on the pain by ANOVA (p=0.0054). The mean VAS score was 24 mm in the cream group and 19 in the patch group (p=0.72). For all other variables, no significant differences were detected.

Study #4 was an open-label, randomized crossover trial at a single center. 31 children ages 4-16 received either 2.5 grams EMLA cream covered with a Tegaderm or the unit-dose patch applied to the antecubital fossa 60-180 minutes prior to venipuncture. At a second visit the subject crossed over to the opposite treatment. A Verbal Rating Scale (no, mild, severe pain) was used. Local skin sensations (itching, burning) were rated by the patient on a four-point VRS (none, mild, moderate, severe). Local skin reactions of pallor, redness, edema were also reported by the investigator using the four-point VRS. Degree of affixment of the dressing was rated by the investigator.

Fisher's exact test was used in the analysis, $p< 0.05$ set as significant. 27 patients were included in the efficacy analysis because the remaining four did not crossover to the other treatment. All 31 patients were included in the safety analysis.

There were no differences between the two treatments. 89% of patients using the cream and 100% of patients using the patch reported no/slight pain from venipuncture. All patients reported

no or slight pain from removal of the dressing. No statistically significant difference was found for adhesiveness, local skin reactions, or local discomfort.

Study #5 was presented as a published article (Pediatric Research 32: 520-523, 1992). This was a randomized, open-label, study of 160 children ages 5-18 years old had 5% EMLA cream 2.5 gm covered by a Tegaderm or the unit-dose EMLA patch applied for 60-120 minutes prior to venipuncture for procedures related to treatment of chronic disease in four clinics. A 100 mm VAS scale was used to assess pain from venipuncture and the pain of removing the adhesive bandage. The adhesiveness of the bandage and local reactions were also recorded.

T-test for unpaired data was used to compare age, pain scores, time since last venipuncture, and application time of treatment. ANOVA for repeated measures was used to compare three pain scores: pain of last puncture, pain of removing the dressing, pain of venipuncture. Stepwise regression analysis was used to define correlation between age, time since diagnosis, and time since last puncture with pain scores. Sample size was calculated to detect a difference of 5 points on the VAS scale, assuming a SD= 12.5, α=0.05, and β=0.20.

Pain from venipuncture was not significantly different between treatment groups (patch: 8.5 $\pm$ 16, cream: 9.5 $\pm$ 17) and both treatments reduced pain from venipuncture experienced at the last visit. The patch was incompletely affixed to the skin in 14 cases and the Tegaderm was incompletely affixed in 5 cases (p=0.026). There were no differences in local reactions or discomfort at the site of application. A significant correlation was observed between pain experienced and 1) age, 2) time since diagnosis. 80% of children said they would wish to receive EMLA for their next puncture.

Reviewer's Comments

Five studies, comparing the efficacy of the EMLA patch, containing 1 gm of EMLA cream, to the usual clinical dose of 2.5 gm EMLA Cream under a Tegaderm dressing were presented, support the clinical equivalency of these two preparations. Because of the differences in thickness and elasticity, the adhesiveness of the patch is not uniformly as reliable as that of the Tegaderm dressing; however, the effectiveness of the patch was not affected. The degree of anesthesia achieved is directly related to the duration of application of the cream or patch, again with no significant differences distinguishing between the two preparations. Common irritations reported by patients during the use of EMLA cream are stinging, tingling, itching and burning. These occurred with equal frequency with both preparations. Likewise the observation of common local skin effects - pallor, redness, and edema at the site of the anesthetic, and redness at

the site of the adhesive - were observed with equal frequency with both preparations.

Conclusions

The sponsor has presented multicenter data which support the efficacy and safety of the EMLA unit dose disk as clinically equivalent to EMLA Cream when applied according to directions.

/S/

Please sign →

Roberta C. Kahn, M.D. Date 7/29/97

Peer Reviewer Date

NDA 19-941, SR-004
HFD-170/Div File/ R. Kahn/ K. Nolan

/C Wright/

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

NDA # 19-941
EMLA Cream and EMLA Anesthetic Disc
Review of Final Draft Labeling
Medical Reviewer's Addendum to Draft Labeling

Received for Review:	**December 17, 1997**
Date of Review:	**December 17, 1997**
Medical Reviewer:	**Roberta C. Kahn, M.D**

The following additional information discussing pediatric use are recommended. Reviewer's comments appear in *"italics."*

CLINICAL STUDIES

Insert after third paragraph:

Insert after: Local dermal effects...transient in nature.

Pediatric Use:

Insert the following:

Controlled clinical studies of EMLA Cream in children under the age of seven years have shown less overall benefit than in older children. [1-3] These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

1. Robieux I, Kumar R, Radhakrishnan S, Koren G. Assessing pain and analgesia with a lidocaine-prilocaine emulsion in infants and toddlers during venipuncture. J. Pediatr 1991; 118: 971-973.

2. Hallen B, Carlsson P, Uppfeldt A. Does lidocaine-prilocaine cream permit painfree insertion of iv catheters in children? Anesthesiology 1982; 57: 340-342.

3. Maunuskela E-L, Korpela R. Double-blind evaluation of lignocaine-prilocaine cream (EMLA) in children. Br J Anaesth 1986; 58: 1242-1245.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-962

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #3	Organization FDA/HFD-170	NDA Number 19-941
Name and Address of Applicant: Astra USA Inc. 50 Otis Street Westborough, MA 01581-4500 tel.: 508-366-1100 Attn: Paul J. Damiani, Ph.D. Ass. Dir. Reg. Affairs		**AF Number** **Supplement Number Date** SCP-004, 7/14/95
Name of Drug EMLA Cream	**Nonproprietary Name** Lidocaine and Prilocaine Cream	**Amendment & dates** AC 12/19/96
Supplement Provides for a unit-dose container of and a change in the formulation.		**Related INDs, NDAs and DMF**
Pharmacological Category dermal analgesic for topical use on intact skin.	**How Dispensed** Rx X	
Dosage Form: Cream	**Potency:** Lidocaine 2.5%w/w & Prilocaine 2.5%w/w 5 and 30 g of cream per tube 1 gram per unit-dose (Anesthetic Disks)	
Chemical Name and Structure See USAN 94 pages 378 & 545.		**Records & Reports Current** yes no **Reviewed** yes no

COMMENTS:

CONCLUSIONS and RECOMMENDATIONS:
It is recommended that approval be granted to this supplemental application. An acceptable recommendation for the facility was issued by the compliance on 10/17/97. See attachment.

CC:
NDA 19-941
HFD-170/Division File
HFD-170/MTheodorakis
HFD-170/KNolan
HFD-170/ADSa: 11/20/97
R/D Init. by:
F/T by:MCT/
DOC.\ASTRA\19941-04.SU3.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Michael C. Theodorakis Ph.D.	/S/	11/19/97

Distribution: Original Jacket Reviewer Division File

CHEMIST'S REVIEW #2	Organization FDA/HFD-170	NDA Number 19-941
Name and Address of Applicant: Astra USA Inc. 50 Otis Street Westborough, MA 01581-4500 tel.: 508-366-1100 Attn:| Paul J. Damiani, Ph.D. Ass. Dir. Reg. Affairs		**AF Number** **Supplement Number Date** SCP-004, 7/14/95 **Amendment & dates** AC 12/19/96
Name of Drug EMLA Cream	**Nonproprietary Name** Lidocaine and Prilocaine Cream	
Supplement Provides for a unit-dose container of and a change in the formulation.		**Related INDs, NDAs and DMF**
Pharmacological Category dermal analgesic for topical use on intact skin.	**How Dispensed** Rx X	
Dosage Form: Cream	**Potency:** Lidocaine 2.5%w/w & Prilocaine 2.5%w/w 5 and 30 g of cream per tube 1 gram per unit-dose (occlusive dres)	
Chemical Name and Structure See USAN 94 pages 378 & 545.		**Records & Reports Current** yes no **Reviewed** yes no

COMMENTS:

CONCLUSIONS and RECOMMENDATIONS:

The Applicant provided satisfactory responses to the chemistry deficiencies of the Agency's letter dated August 8, 1996. This supplement is approvable provided a satisfactory EER is received from Compliance.

CC:
NDA 19-941/S-004
HFD-170/Division File
HFD-170/MTheodorakis
HFD-170/KNolan
HFD-170/ADSa: 8/5/97
R/D Init. by:_____
F/T by:MCT/_____
DOC.\ASTRA\19941-04.SU2

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Michael C. Theodorakis Ph.D.	/S/	8/4/97

Distribution: Original Jacket Reviewer Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-962

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-941	**Supplement**: SLR-004 **Related IND**
Name: EMLA Cream	
Sponsor: Astra Pharmaceutical Products, Inc., 50 Otis St., Westborough, MA 01581	
Submission Date: July 14, 1995	
Reviewer: Suresh Doddapaneni, Ph.D.	**Review Date**: December 15, 1997

SYNOPSIS

EMLA Cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% which is indicated for dermal anesthesia. About 2.5 gm of the cream is applied over a 2 X 2 sq. inch (25 sq. cm) area of the skin and is covered by Tegaderm occlusive dressing. Astra has developed an EMLA unit-dose disk which is a single-dose unit of EMLA contained within an occlusive dressing (composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring). The formulation was slightly modified in the cream used for making the disk, in that the concentration of the thickening agent, Carbomer 934P, has been decreased from %.

The following points illustrate the possible ways in which the disk might differ from the Cream with a possible affect on its clinical performance resulting in the patch being considered a new dosage form;

(1) In the case of Cream, it is applied on the skin and is then covered by Tegaderm dressing.

(2) In the case of the disk, same amount of the modified cream is absorbed into a cellulose disc with a laminate backing (aluminum foil with plastic film on both sides) and an adhesive tape ring. This has the following implications on the overall release of the two drugs into the skin;

   (a) The thermodynamics of drug release may be different. For example, because cellulose pad absorbs moisture and swells, the movement of drug molecules absorbed deep in the cellulose pad may be slowed down because of the cellulose fibers.

   (b) Since the occlusive dressing is different, its affect on the hydration of the skin may be different and is unknown.

   (c) Since the viscosity of the cream used in the disk is lower, leakage on use may occur.

   (d) The local irritability and the degree of adhesiveness of the adhesive may be different.

The Sponsor conducted an *in vitro* skin permeation experiment to show that release rates are equivalent. However, this study can be used only as supportive information, since the disk was modified to facilitate the experiment. Among other things, the backing film used in this experiment was HY-BAR polymer rather than aluminum/Suralyn laminate used in the original disk. Thus the occlusion affects of the aluminum/Suralyn backing could not be evaluated in this experiment. The systemic levels that are seen after EMLA Cream application are substantially low and it would be

expected that the systemic levels after the application of the disk, even if different, would be also be lower. Therefore, the main concern from a clinical point of view would be efficacy (local) and not safety (systemic). The sponsor conducted five clinical studies (86-EM-11, 89-EM-01, 89-EM-04, 62-15, and 62-09) comparing the efficacy of EMLA Cream and the EMLA unit-dose disk and these studies should be used in the approval decision making process.

/S/ 12/16/97

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
DPE II/OCPB

FT initialed by Dale Conner, Pharm.D.: 12/16/97

CC:

NDA 19-941 (Original), HFD-170 (Nolan), HFD-850 (Lesko, Huang), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner), HFD-340 (Viswanathan) CDR (Barbara Murphy).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-962

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: December 9, 1997

FROM: Dr. Michael C. Theodorakis, Senior Review Chemist, HFD-170 12-9-97

TO: NDA 19-941/SCP-004 submission dated November 11, 1997

SUBJECT: Chemistry Comments on Labeling

THRU: Dr. Albinus D'Sa, Chemistry Team Leader, HFD-170 12/9/97

The Description and How Suppled sections of the proposed labeling for EMLA Cream packaged in tubes and Anesthetic Disc are adequate from the chemistry standpoint.

On the Carton Labeling on page 43a, the word should be replaced by

CC:
NDA 19-941/S-004
Div. File

DOC:

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administrations
Center for Drug Evaluation and Research

Date: January 5, 1998

From: Cynthia McCormick, M.D.
Director,
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

To: File NDA #19-941/SLR-004 /Division File
and
Paula Botstein, MD
Director,
Office of Drug Evaluation III
HFD-103

Subject: Approval of EMLA Anesthetic Disc

This memorandum conveys for the file the basis for the Division's decision for an approval action to be taken on NDA #19-941/SLR-004 EMLA Anesthetic Disc.

Background

EMLA Cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%, indicated for local anesthesia of the skin. The approved product is applied to the skin (1-5 g) and retained under an occlusive dressing for up to 60 minutes to provide useful surface anesthesia.

The present supplement is for a new unit dosage form characterized as an anesthetic disc in which the cream is imbedded into a cellulose sponge saturated with 1 gram of the cream, surrounded by an adhesive polythethylene foam ring with the unit adhering to a foil backing. The advantages of the proposed unit dosage form are described by Dr.Kahn in her summary of the sponsor's submission.

As Dr. Doddapaneni, the pharmacokinetics consultant has pointed out this is not simply a unit dose of EMLA cream, but involves a formulation change and the

impregnation of a cellulose disc which might act to alter the thermodynamics of drug release. The Office of New Drug Chemistry has reviewed this application and concurs that this is a new dosage form and this product has been administratively assigned a separate NDA number. For the purposes of convenience the package insert will include information on both products.

The systemic levels seen after EMLA Cream application are substantially low and it would be expected that the levels seen after the Disc application would be just as low. Thus formal bioequivalency studies were not practical for this new dosage form. Therefore, clinical efficacy studies were submitted by the sponsor in which the Anesthetic Disc was compared to EMLA cream and provided equivalent results. These studies mentioned in Dr. Kahn's summary are small equivalence trials. In addition the sponsor conducted an *in vitro* permeation experiment in human epidermis as evidence which showed that the release rates from EMLA anesthetic disc and EMLA 5% cream are equivalent.

The first clinical study was an open label study in 21 patients comparing a dose of 0.8 g EMLA per 9.6 cm^2 Anesthetic Disc with EMLA applied from a tube under a Tegaderm dressing and with unanesthetized skin. In this study 12 doses per patient were tested and application times of 1, 2, 3 and 4 hours were evaluated by pinprick and needle insertion and were compared with unanesthetized skin. Anesthesia was assessed by means of a VAS pain scale of 1 to 100. There was a statistically significant difference between the cream and disc at 60 minutes but both provided clinically and statistically significantly better anesthesia than the unanesthetized skin.

The second study was also an open label parallel group study in 178 children undergoing venipuncture. In this study the EMLA was applied as a disc or as cream (1/2 tube) under a Tegaderm dressing. The cream remained in place for 1-2 hours. The patients were asked to assess the pain of venipuncture using a 3-point verbal rating scale (no pain, slight pain, severe pain). The results of this unblinded study revealed that patients in both groups reported no or slight pain associated with venipuncture 95% in the Disc group and 97% in the cream group. There was no statistically significant difference between the groups. This uncontrolled equivalency trial alone is not considered adequate evidence for efficacy.

A third study performed in 63 children between the ages of 5 and 15 scheduled for inpatient surgery were given either 2.5 g of EMLA cream covered by a Tegaderm bandage or EMLA anesthetic disc on the dorsum of the hand for 60-180 minutes. VAS scores were recorded (0-100) with the pain associated with venipuncture for the placement of an IV catheter. The sponsor's results reported in Dr.Kahn's synopsis did not reveal a significant difference between the pain scores between the two

treatments for what would be considered a painful procedure.

A fourth study was an open label crossover trial in 31 children aged 4-16 who received either the EMLA anesthetic disc or EMLA cream 2.5g covered with a Tegaderm dressing for 60-180 minutes prior to venipuncture. At a second visit treatment was crossed over to the opposite treatment. Pain was reported on a 4-point VRS (none, mild, moderate, severe). There were again no significant differences between the treatments. 89% of patients using the cream, and 100% of patients using the anesthetic disc reported mild or no pain associated with venipuncture.

The clinical trials in support of the efficacy of EMLA anesthetic disc were necessary for the determination of equivalent efficacy of EMLA 5% cream. The FDA's current topical anesthetic guidelines do recommend the use of a control either a placebo or an active control in the determination of efficacy. The active control studies conducted for this new dosage form were not as robust as they might have been had this been a new agent with no proven track record. The first study incorporated a comparison to both dosage forms with with unanesthetized skin and therefore was probably the most convincing comparison with both agents demonstrated a striking difference from the untreated skin. The remaining three studies controlled against EMLA Cream are considered merely supportive although there was arguably an effect when the VAS scores for each application are compared in time.

It is my opinion that while these clinical trials are small and unblinded, there was an effect demonstrated that adequatley establishes the therapeutic equivalence of EMLA anesthetic disc and EMLA cream.

Recommend: Approval of EMLA anesthetic Disc with the attached label.

/S/

Cynthia G. McCormick, MD
January 5, 1998

(121)

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dr. Dan Boring, Chairman, (HFD-530) Corp.Blvd

FROM: Dr. Michael C. Theodorakis,
Division of Anesthetic, Critical Care and Addiction Drug Products
(HFD-170)
tel. 301-443-3741, fax: 301-443-7068

DATE: 2 December 1996

SUBJECT: Request for Assessment of names for a dosage form name
NDA 19-941/S-004

Proposed Trademark:
EMLA Anesthetic Disc
EMLA Medicated Disc
EMLA Disc
EMLA Unit-Dose Disc

Established name, including dosage form:
Lidocaine and Prilocaine Cream

Other trademarks by the same firm for comparison products:
EMLA® Cream

Indications for use (may be a summary if the proposed statement is lengthy):
This is a cream for topical use. It is packaged in unit dose containers. The cream has been sorbed (impregnated) in a cellulose disk. The disk with the cream has been placed in an occlusive dressing which has an adhesive edge (adhesive tape). A laminate has been placed to cover the exposed side of the disk and the adhesive edge of the occlusive dressing. In order to place the occlusive dressing over the skin, the laminate is removed to expose the disk impregnated with cream and the adhesive edge of the occlusive dressing.

Initial comments from the submitter: (concerns, observations, etc.)
Originally, the Applicant wanted to call it patch. This was rejected because it is not a transdermal system. Thi was based on the fact that this drug was not used to cause a systemic effect and the rate of release from th cellulose disk was not controlled.

In USP/23 Chapter <1121> "Nomenclature", drugs for local effect and which are embedded in glue on a cloth c plastic backing are described as "plasters" or "tapes", (see page 1949, USP/23). So this drug product could b called EMLA Plaster or EMLA tape or EMLA Cream Plaster or EMLA Cream Tape.

Please find attached the Appicant's correspondence of 11/21/96 as well as samples of the EMLA cream.unit-do: packages. We request that you consider the names proposed by the Applicant and provided us with your opinio

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at lea one week ahead of the meeting. Responses will be as timely as possible.

CC:
NDA 19-941 jacket/division folder
HFD-170/ADS'a
HFD-170/IKumar

Consult #721 (HFD-170)

EMLA Anesthetic Disc
EMLA Medicated Disc
EMLA Disc
EMLA Unit-Dose Disc

The trademark EMLA is used on an approved product and was not considered by the Committee. Of the choices submitted for descriptive nomenclature, the Committee preferred "Anesthetic Disc" or "Disc". The Committee felt the most appropriate established name for this product is prilocaine and lidocaine cream topical adhesive system.

The Committee has no reason to find the proposedproprietary name unacceptable.

2/5/97, Chair
CDER Labeling and Nomenclature Committee

NDA

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-962 Supplement #_____

HFD-170 Trade and generic names/dosage form: EMLA Cream(lidocaine 2.5% and prilocaine 2.5% in a new dosage form, a single dose unit of EMLA® contained within an occlusive dressing for use as a topical anesthetic on normal intact skin for local anesthesia. Action: AP

Applicant Astra USA, Inc Therapeutic Class 6S

Indication(s) previously approved as a topical anesthetic for use on normal intact skin for local analgesia.
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application for the marketing of EMLA7 (lidocaine 2.5% and prilocaine 2.5%) in a new dosage form, a single dose unit of EMLA7 contained within an occlusive dressing for use as a topical anesthetic on normal intact skin for local anesthesia. (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___ c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Signature of Preparer and Title/Date

Project Manager/CSO/Date 11/28/01

cc: Orig NDA/PLA/PMA # 20-962
HFD-170 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at

Division of Anesthetic, Critical Care, and Addiction Drug Products

CONSUMER SAFETY OFFICER LABELING REVIEW NDA 20-692

(previously NDA 19-941/S-004)

Application Number: NDA 20-962 **(previously NDA 19-941/S-004)**
Name of Drug: EMLA (lidocaine 2.5 % and prilocaine 2.5) Cream
Sponsor: Astra USA

Material Reviewed

Submissions Dated:

Previously Supplement-04 to NDA 19-941
November 21, 1996, received November 22, 1996
December 19, 1996, received December 20, 1996

Previously SCP-004 BL to NDA 19-941
November 7, 1997, received November 10, 1997
(electronic labeling submission for NDA 19-941/S-007 and S-009)

SNC
December 3, 1997, received December 4, 1997
(electronic labeling submission for NDA 19-941/S-008)

Background and Summary Description: To expedite the review of NDA 19-941/S-007, NDA 19-941/S-009, and NDA 19-941/S-008 the applicant was requested to submit an electronic submission of labeling for each of the above listed supplements. The electronic submissions dated November 7, 1997 and December 3, 1997 are certified by the sponsor to be the identical version that was sent originally in hardcopy.

This NDA (previously NDA 19-941/S-004) addresses a change in packaging (i.e., the addition of the "disc" dosage form to the originally approved occlusive dressing and cream dosage form). The Nomenclature Committee preferred "Anesthetic Disc" or "Disc'' as conveyed February 5, 1997 (Attachment 1).

Review:

A comparative review of the last approved labeling as cited in the Agency's April 11, 1994 approval letter to each of the above listed supplement submissions resulted in the following specific changes noted in Attachment 2. These labeling submissions provide for significant labeling changes that either clarified or updated information already in the insert.

Attachment 2 contains strikeouts, underlines to the November 7, 1997 electronic submission. These changes were made by the Division Director and other reviewers, based on their review of labeling.

Attachment 3 contains the "final" draft labeling which will be sent to the applicant with the action letter.

Please note, the applicant's adherence to the Nomenclature Committee's preference for use of "Anesthetic Disc" or "Disc'' was noted in the above labeling submissions.

The medical, chemist, and pharmacokinetic reviewers concur that this NDA 20-962 (previously NDA 19-941/S-004) labeling submission be approved. Concerning NDA 20-962 (S-004) labeling, please note that medical reviewer stated, "no recommendations for further changes to this labeling with," per December 3, 1997 e-mail message. The pharmacokineticist stated, "no pk comments but somewhere in the label they should link up both products (similar efficacy or something of that nature). The chemistry reviewer suggest "on the carton labeling ... the word 'hydrox-ide" should be replaced by "hydroxide." Attachment 4 contains these reviews.

I recommend concurrence to these reviewers' suggested revisions.

Finally, it is strongly recommended that the applicant use of the terms
and the use of latest approved dosage form
should be consistently and appropriately used through the insert.

Conclusions: Recommend approval of labeling as stated in Attachment 3.

/S/ 1/30/98
Consumer Safety Officer

Supervisory Comment/Concurrence:

/S/
Consumer Safety Officer

cc:

Original
HFD-170/Div. Files
HFD-170/KEN
HFD-170/Moody
HFD-170/KhanR
HFD-170/SDoddapaneni
HFD-170/MTheodorakis
HFD-170/CMcCormick, M.D.

draft: /December 11, 1997/January 27, 1998/A:\20962lbl.cso
Initials:
final:
CSO REVIEW

ADMINISTRATIVE
MEMORANDUM TO FILE
NDA 19-941 AND 20-962

February 4, 1998

Re: Creation of NDA 20-962 and Applicability of NDA 19-941 S-007, SE4-008, and S-009 Files to NDA 20-962

Per the attached approval letter dated, February 4, 1998, NDA 19-941 SCP-004 was converted to NDA 20-962 as stated in the letter. To confirm to the bundling policy, this memorandum serves as documentation that the application, Office of Financial Management, COMIS, and the charge/history card documents have been revised to reflect these changes.

SCP-004 was originally submitted as a supplemental application to NDA 19-941. We have reclassified the former supplemental application as NDA 20-962 to conform to the "Interim Guidance on Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992". The guidance specifies that, "Different dosage forms should be submitted in separate original applications unless the products are identical (drugs) or alike (biologics) in quantitative and qualitative composition."

S-008 was submitted as a supplemental labeling revision but is actually an efficacy supplement, per medical reviews.

Please note that the supplemental labeling revisions applicable to S-007 and S-009 apply equally to NDA 19-941/S-008 and NDA 20-962. Since these supplements pertain to the original and new dosage forms.

These decisions were recommended per HFD-103, HFD-002 (Dr. Murray Lumpkin) and the Office of Financial Management.

Attached is the November 24, 1997 action plan in which these administrative changes were derived.

NDA 19-941 and NDA 20-692
Documentation of Teleconference
February 20, 1998

FDA Attendees
Hal Blatt, Regulatory Project Manager
Ken Nolan, Project Manager

Astra Attendee:
Brian Green
Regulatory Affairs Specialist

In response to Astra's February 13, 1998 facsimile regarding draft labeling for NDA 19-941 and NDA 20-962 that was attached to the February 4, 1998 action letter, the Agency agrees with Astra's rationalization for making the three proposed changes stated in the facsimile before preceding with the final printing labeling. Per the Division Director's approval, the three proposed labeling changes and the teleconference were implemented. No other action is required from Astra or the Agency other than Astra submitting the final printed labeling incorporating the three proposed changes.

cc: NDA 19-941
NDA 20-962
Div. Files
HFD-170/HBlatt

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-962

CORRESPONDENCE

ASTRA®
Astra USA

NDA 20-962
EMLA® Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5% cream) Topical Adhesive System

GENERAL CORRESPONDENCE

February 13, 1998

Cynthia McCormick, MD, Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
ODE III, CDER, FDA
HFD-170, Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. McCormick:

Reference is made to NDA 20-962, EMLA Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5% cream) Topical Adhesive System, approved February 4, 1998. Reference is also made NDA 19-941, EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%), specifically three supplemental applications identified as S-007, S-008 and S-009. These supplements, also approved on February 4, 1998, provided for various labeling revisions.

Included with the approval letters for NDA 20-962 and the referenced supplements was draft package insert labeling which reflected the proposed changes of all these applications as well as revisions made by the Division to Astra USA's proposals. The approval letters dictate that final printed labeling must be submitted which is identical to the draft labeling provided.

In reviewing the Division's draft labeling, Astra USA has noted a few inconsistencies and a minor error which we would like to bring to the Division's attention before proceeding with final printed labeling. In addition, Astra USA would like to propose two minor clarifications. Attached with this letter is a description of the observations made in reviewing the package insert and Astra USA's proposal to deal with them.

A teleconference has been scheduled for Friday, February 20, 1998 at 11:30 AM to discuss these minor modifications. Since this labeling reflects both EMLA Cream and EMLA Anesthetic Disc, it is Astra USA's hope that these issues can be resolved during the teleconference, so as not to delay the launch of the EMLA Anesthetic Disc. An identical letter is being sent to NDA 19-941, EMLA Cream.

If you have any questions regarding this application, please do not hesitate to contact me at (508) 836-8488 or Paul J. Damiani, Ph.D. (508) 366-1100, ext. 4772.

Sincerely,

Brian A. Green

Brian A. Green
Regulatory Affairs Specialist
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