CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 19-941/S-008

Trade Name: EMLA CREAM

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

Sponsor: Astra USA, Inc.

Approval Date: February 4, 1998

Indication: Provides for pre-procedural application of EMLA Cream to adult male genital skin prior to site-specific subcutaneous infiltration with lidocaine for the removal of genital warts.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 19-941/S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 19-941/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-941/S-008

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 supplemental New Drug Application (sNDA) dated November 5, 1996, received February 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%).

The User Fee goal date for this application is February 25, 1998.

The supplemental application provides for pre-procedural application of EMLA®Cream to adult male genital skin prior to site-specific subcutaneous infiltration with lidocaine for the removal of genital warts.

This supplement was originally submitted as a supplemental labeling revision application to NDA 19-941. We have reclassified the former supplement as an efficacy supplemental application to conform to Agency policy.

We have completed the review of this supplemental 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 19-941/S-008. 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.

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

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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 Manager, at (301) 443-3741.

/S/

Sincerely.

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

ENCLOSURE

cc:

Original NDA 20-962
NDA 19-941
HFD-170/Div. files
HFD-170/CSO/KNolan
HFD-170/CMoody
HFD-170/AD'Sa
HFD-170/MTheodorakis
HFD-170/RKahn
HFD-170/CMcCormick
HFD-720/JMa
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: //KEN/December 3, 1997/January 15,1998/January 20, 1998/January 23,1998/January 29, 1998/February 4, 1998/m:/n19941a.d12
Initialed by:
final:

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-941/S-008

MEDICAL REVIEW(S)

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

NDA # 19-941
Supplemental Application SLR-008

Application for Revision of Labeling for EMLA® Cream

Date of Submission: November 7, 1996
Date of Review: December 9, 1996

The sponsor has submitted proposed labeling to indicate a new indication for EMLA® Cream. The amended labeling specifies pre-procedural application of EMLA® Cream to adult male genital skin prior to site-specific subcutaneous infiltration with lidocaine for removal of genital warts.

The labeling claim is supported by the results of study protocol #93-EML-18 (IND . entitled "A Randomized Open-Label, Comparative, Parallel Group Study to Evaluate the Efficacy and Safety of EMLA® Cream and 1% Xylocaine® Infiltration in Males for Relief of Pain Associated with Removal of Genital Warts by Cryotherapy." The final study report was reviewed on 9/27/96.

The proposed labeling claims are supported by the clinical data from this study. The proposed wording appropriately excludes the use of EMLA® Cream prior to circumcision in pediatric patients.

The labeling claim is reasonable from a medical review standpoint.

/S/

Roberta Q. Kahn, M.D. — 12/11/96
Date

/S/

Peer Reviewer — 11 December 1996
Date

NDA #19-941
HFD-170/ Div File
HFD-170/ M. Wright
HFD-170/ R. Kahn

Team Leader Review

NDA 19,941 SLR-008
Astra, USA
EMLA Cream Amendment (Genital Warts)
Letter Date of Submission 11/05/96
Initial PDUFA Date: 5/05/97
Correct PDUFA Date: 11/07/97
Date Received for Review 7/22/97
Date Review Completed : 7/25/97
Reviewer: Curtis Wright MD
Peer Reviewer: R Kahn, MD

Attachments:

#1 - Review, NDA 19-941 SLR 008, Roberta Kahn, dated 12/11/96
#2 - Review, NDA 19-941 SLR 008, Jonathan Ma, dated 4/22/97
#2 - Summary tables, Pharmacokinetic subgroup, SLR 008

Abstract

This application was filed as a labeling amendment (SLR-008), but actually is an Efficacy Supplement which contains clinical data supporting the use of EMLA cream as a pre-anesthetic prior to local anesthetic infiltration for removal of genital warts.

The data supports the sponsor's claim that EMLA is effective in this new application of the product.

What was reviewed?

This material was contained in jackets 1-3 of SLR 008 consisting of proposed labeling changes, and clinical data from a comparative study funded by the sponsor. The sponsor conducted a randomized, open-label, comparative, three-arm, parallel-group study of lidocaine anesthesia, lidocaine with EMLA pre-treatment, and EMLA anesthesia alone prior to cryotherapy for removal of genital warts.

What is the sponsor's specific request?

The sponsor wishes to add pharmacokinetic data on the absorption of EMLA from genital skin, a description of the clinical trial, a precaution not to use EMLA for infant circumcision, and dosing instructions for use of EMLA on genital skin.

What are the facts as we know them?

EMLA background- EMLA cream is a eutectic mixture of lidocaine and prilocaine which was approved in the early 90's for topical anesthesia on intact skin prior to local anesthesia. Efficacy depends on the permeability of the skin, the thickness of the application, the duration of application, and the degree of occlusion (occlusive application is usually required). EMLA is generally safe, though excessive application can result in methemoglobinemia due to prilocaine metabolism, especially in the very young or congenital methemoglobinemics. The safety and efficacy of EMLA has usually been tested in settings where efficacy is obvious (surgical stimuli), and safety has been shown by systemic lidocaine absorption and percent concentration of methemoglobin.

Trial Design- This is was an open-label, three -group, parallel-group, randomized, controlled clinical trial of EMLA, EMLA & Lidocaine injections, and Lidocaine injections alone as pre-operative anesthesia for cryotherapy of male genital warts. The protocol called for 15 minutes of occlusive application of EMLA (groups 1 & 2), followed by 1% lidocaine (groups 2 & 3), followed by

cryotherapy. Patients rated their pain using a 100 mm VAS scale immediately after application of EMLA cream, immediately after local anesthetic infiltration, and at the end of the procedure. Twenty-one additional subjects at the end of the trial underwent a nested PK analysis of serum lidocaine levels.

Patient Selection and Disposition- Patients were male, between 18-65 years of age, and had penile warts. Patients with active infections, overlying skin disorders, repeat cryotherapy patients, patients taking narcotics, and known methemoglobinemics were excluded.

Patient Disposition	EMLA	EMLA/Lidocaine	Lidocaine
Enrolled	41	40	40
Male	41	40	40
Caucasian	27	29	27
Black	14	8	11
Other	0	3	0
Age(SD)	30 (8)	32 (8)	31 (9)
ASA I	40	38	39
ASA II	1	2	1
Completed	41	40	40

Treatment- "Half a tube" (2.5 grams of a 5 gram tube) was applied 15 minutes before injection of cryotherapy. If the lesion was not under the foreskin, Saran Wrap was applied as occlusion.

Allocation of treatment was as follows:

	EMLA	EMLA +Lidocaine	Lidocaine Only
	41	25 (one injection)	31 (one injection)
		11 (two injections)	6 (two injections)
		4 (three injections)	1 (three injections
		0 (four injections)	2 (four injections)
Mean Lidocaine Injected		0.7 (0.3) ml	0.5 (0.4) ml

As may be noted, there were five more patients with multiple sites in the EMLA + Lidocaine group than in the Lidocaine group, resulting in a slightly larger mean dose. The difference is not sufficient to significantly bias the results.

Concomitant medications were limited to antibiotics and multivitamins, and there appear to be no confounding analgesics (one patient was taking ibuprofen).

Protocol Deviations- One patient took amytriptyline and was excluded (EMLA group) and one VAS for one patient was mis-timed by 10 minutes (Lidocaine group) and was not excluded. Both were consistent with the protocol.

Efficacy Results

Mean (SD)	EMLA	EMLA/Lidocaine	Lidocaine
Mean VAS after EMLA	0.7 (2) mm	0.3 (1.2) mm	N/A
Range			
% with no pain	80%	90%	
Mean VAS after Injection		6.8 (9) mm	14.3 (16) mm
Range			
% with no pain		45%	7.5%
Mean VAS after Surgery	24.8 (21) mm	2.3 (6) mm	6.5 (10) mm
Range			
% with no pain	5%	65%	32.5%

Attention is directed to Dr. Ma's statistical review (page 3). His first conclusion was that EMLA did not provide adequate relief from pain during cryotherapy. I agree. His second conclusion was that EMLA pretreatment may have improved the overall outcome slightly, but clearly reduced the pain of the lidocaine injections. I agree with this interpretation as well, but feel that the overall outcome was improved, albeit slightly..

Efficacy discussion- This drug is already approved for pre-treatment of injection sites. Had the sponsor claimed that the EMLA alone was effective, this open label trial would be difficult to interpret since it has few internal controls to prevent bias. Since it is hard to conceive of investigator's biasing the trial against the sponsor's product, and the facts of an already high expectation that the drug will be effective, the clear failure of EMLA as an operative anesthetic suggests that this trial was sensitive, and acceptably unbiased. By our usual criteria, this trial had about a 20 mm spread between the most divergent groups, with a between-patient pooled standard deviation of about 12 mm, and a consequent effect size of about 1.6 standard deviations, typical for a successful anesthetic/analgesic trial.

Safety- Genital skin, (especially scrotal and sub-pudental skin) is thinly cornified, and there should be a concern that there is a risk of excessive absorption. The nested PK safety study looked at the lidocaine and prilocaine absorption, as contrasted with 10 mg IV test doses of each component (N=20): Bloods were sampled at baseline, 10, 20, 30, 45 min and 1,2,3,4,5 and 6 hrs after dosing. The doses varied considerably(note varying EMLA dose v. 10 mg IV dose):

Subject	Dose EMLA	mg Cream	AUC Cream/IV/F Lidocaine	AUC Cream/IV/F Prilocaine	Cmax Cream/IV Lidocaine	Cmax Cream/IV Prilocaine
	0.3 gm	7.5	48/242 (31)	9/68 (6)	5/273	2/75
	0.4 gm	10	45/134 (39)	16/56 (6)	6.9/82	3/35
	0.5 gm	12.5	26/193 (13)	1/56 (6)	4.2/363	2.6/91
	0.4 gm	10	12/219 (6)	missing/62	2.9/136	missing/231
	0.3 gm	7.5	missing/136	missing/ 55	missing/64	missing/34
	0.6 gm	15	15/174 (6)	missing/69	3/920	missing/1202
	0.4 gm	10	6/132 (20)	10/55 (9)	6/197	4/98
	0.5 gm	12.5	10/142 (7)	missing/64	2.5/218	missing/293
	0.6 gm	15	41/148 (21)	8/78 (4)	5/282	2.7/119
	0.6 gm	15	24/144 (12)	7/85 (4)	5/288	2.5/122
	0.8 gm	20	28/150 (11)	12/76 (5)	6/116	4.0/50
	3.2 gm	80	42/191 (3)	missing/missing	11/432	6.4/missing
	3.3 gm	82.5	33/255 (2)	missing/missing	5/268	5.4/missing
	0.6 gm	15	42/176 (18)	9/102 (4)	16/264	2.9/198
	0.4 gm	10	49/616 (9)	4/292 (3.5)	8/7912*	3.5/8218*
	0.2 gm	5	missing/263	missing/63	missing/584	missing/160
	0.4 gm	10	41/180 (26)	13/75 (9)	7/193	5/161
	0.8 gm	20	41/185 (26)	11/808 (3)	7/193	4/32076*
	2.2 gm	55	53/138 (13)	7/42 (4)	14/334	4/37
	1.4 gm	35	8/106 (2)	missing/38	3/74	7/19
Median	0.9 mg	22 mg	37/196 (14)	11/67 (6)	6/278	4/121

The analyses were performed using using Astra standards, the lower limit for the method was 2.5 ng/ml, with daily standards ranging from ng/ml and log 10 dilutions as needed to keep the signal in range. Examination of the outliers, e.g. patient 19, sample 41931, shows that the sponsor provided no explanation for patients who were supposed to have had blood levels above the toxic level for both lidocaine and for prilocaine. Examination of the protocol shows it calls for indwelling catheters in both arms, and the most logical explanation is that one IV was lost, and the sample was taken out of the arm used to administer the drug. In addition, the Cmax blood levels following EMLA administration are only 1-2 times the lower limit of quantification in many cases.

The PK analysis was done by As the accuracy of the elimination rate constant could only have been poorly estimated by blood levels marginally above the lower limit of quantification, the accuracy of these values are suspect.

Mean(SD)	EMLA		Lidocaine 10 mg	Prilocaine 10 mg
	Lidocaine	Prilocaine		
AUC 0-6 ng/mL*hr	19 (11)	5.5 (6)	163 (95)	109 (180)
Cmax	6.6 (4)	3.9 (1.5)	714 (1713)	2401 (7648)
Bioavailability0-6 hr	9.3 (8)	2.2 (2)		
Bioavailability 0-inf.	13.8 (1)	6.0 (3)		

Despite the deficiencies, the main points of the PK study are clear. The amount of each drug absorbed from the applied mean dose (0.9 grams EMLA or 20 mg lidocaine/20 mg prilocaine) was much lower than the levels corresponding to the IV dose. The sponsor's evaluations of the extrapolated systemic bioavailability for EMLA, were spot checked, and appear correct, but inaccurate to assay and outlier problems (see enclosed summary tables), and subject to the caveats discussed above. The more clinically relevant ratio of Cmax EMLA/ Cmax IV (predictive of toxicity) was 2-4 % based on the mean doses in the table above, which represents a peak blood level ratio of about 1-2 %, after correcting for the relative doses of 20 mg for EMLA and 10 mg for the IV arm.

No clinical methemoglobinemia was observed, and no blood levels were performed.

Deaths, Discontinuations and Serious AE's- One PK patient disenrolled from the later limbs of the PK study.

Non-Serious Safety- There were some non-serious AE's during the study, which are summarized below:

Subject	Event	Outcome
	Chill	Recovered after 1 min
	Sore throat/Congestion	Recovered
	Mild hypertension	Recovered w/o Rx
	Headache	Recovered
	Pallor/SOB during injection	Recovered < 2-5 min.

Comments

EMLA does not provide adequate analgesia for painful male genital procedures, but is effective in reducing the pain from injections of local anesthetic (its indicated usage). There appears to be no increased risk from use in this setting beyond the current labeling.

The PK study appears to support qualitative statements, but not quantitative statements.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Curtis Wright, Deputy Director, HFD-170

1/25/97

CC: NDA 19-941
Division File HFD-170
CSO ~~D Morgan~~ K NDAM
Medical Officer R Kahn

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19-941/S-008

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 19-941/S008
Drug name: EMLA Cream
Applicant: Astra USA, Inc.
Indication: Pre-procedural application to male genital skin prior to site-specific subcutaneous infiltration with lidocaine for removal of genital warts

Documents reviewed: volumes 32.1-3 dated 5 November 1996
(Received HFD-170 7 November 1996)
Medical officer's review
Reviewer: Z. Jonathan Ma, Ph.D., HFD-720
Date of Review: 22 April 1997

Project manager: Millie Wright
Medical reviewers: Roberta C. Kahn, M.D.

Introduction

EMLA Cream, a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin. In this NDA supplement, the sponsor conducted clinical studies to investigate the efficacy and safety of EMLA Cream combined with 1% Xylocaine infiltration for the relief of pain associated with the removal of genital warts in males by cryotherapy.

The clinical studies in this NDA supplement contain two parts. Part I was an open-label, randomized, comparative, parallel group study to compare the efficacy of dermal analgesia when using (a) EMLA alone, (b) EMLA prior to 1% Xylocaine infiltration, and (c) 1% Xylocaine infiltration alone. Part II was an open-label, non-randomized pharmacokinetics study. This review will focus on the randomized efficacy study in Part I.

Clinical Study

One hundred and twenty-one (121) subjects were enrolled to the study. There was one protocol violator who took a psychoactive drug within 3 days of starting the study. Thus, 120 subjects were evaluable for efficacy and 121 evaluable for safety.

Male patients between 18 and 65 years of age who were ASA Risk Classification I and II and scheduled for cryotherapy to remove genital warts were eligible for the study. Also, their skin over the wart site appeared normal. They were mostly caucasions (69%), followed by blacks (27%) and others (4%).

Subjects would be excluded if
1) they had undergone any genital wart removal procedure before, or if they had been involved in any study of another investigational drug within 1 month prior to enrollment; or if
2) they were known to have a congenital or idiopathic form of methemoglobinemia; or if
3) they were known to have used psychoactive drugs, including narcotic analgesia, within the previous 3 days; or if
4) they had used alcohol or medicine containing alcohol within the 12 hours prior to surgery, or if
5) they had known psychiatric, visual or neurologic disorders, which, in the opinion of the investigator, precluded them from making valid assessments of perceived pain; or if
6) they had an allergy to local anesthetics of the amide type or to the constituents of EMLA Cream; or if
7) they had previously enrolled in this study; or if
8) they, in the opinion of investigator, for any other reason, would not comply with the condition of the study; or if
9) they were with any condition what precluded adequate venous sampling; or if
10) they were with genital wart(s) from condyloma lata.

Subjects were randomized to one of the following three treatment groups:

1) EMLA only, where subjects had EMLA Cream applied to the area with the genital wart(s) for 15 minutes followed by the surgery;
2) 1% Xylocaine infiltration only, where subjects received injection of 1% Xylocaine 10 minutes before surgery;
3) EMLA prior to 1% Xylocaine, where subjects had EMLA Cream applied first, followed by injections of 1% Xylocaine 15 minutes later, followed by surgery 10 minutes later.

A Visual Analog Scale (VAS) was used to ask subjects to record the pain intensity experienced. These scales are a 100 mm in length line with "0" for "no pain" and 100 for "worst pain ever". The pain assessments were made immediately following:

a. The application of EMLA Cream (VAS1)
b. The Xylocaine injection (VAS2), and
c. The cryotherapy surgery (VAS3).

Therefore, VAS3 were observed for the subjects in all three treatment groups, while VAS1 were only observed for group 1 and 3, and VAS2 only for group 2 and 3.

Statistical Analysis on Pain Scores

The VAS scores evaluated at three time points are not normally distributed. Thus, nonparametric methods are used to do the comparisons between treatment groups. The following table presents the results from Wilcoxon two-sample test (W) for pairwise comparisons and those from Kruskal-Wallis test (K) for multiple comparisons.

Pain Score median (range)	Treatment Group			P-value
	EMLA only	Xylocaine only	EMLA+Xyl.	
VAS1	0		0	0.19 (W)
VAS2		9.5	1.0	0.002 (W)
VAS3	17	1.5	0	0.0001 (K)
Pairwise Comparisons for VAS3	17	1.5		0.0001 (W)
	17		0	0.0001 (W)
		1.5	0	0.005 (W)

The significant difference in VAS2 between Xylocaine only group and EMLA prior to Xylocaine group ($p=0.002$) implies that the prior use of EMLA significantly reduced the pain associated with the Xylocaine infiltration. EMLA only group experienced much higher VAS3 scores than other two groups, suggesting that EMLA alone does not provide satisfactory local anesthesia for cryotherapy. EMLA prior to Xylocaine group had significantly lower VAS3 scores than Xylocaine only group ($p=0.005$), indicating that the prior use of EMLA may provide an enhancement for the local anesthesia for the surgery procedure, although the improvement in pain score was quite small (median decreased from 1.5 mm to 0, out of 100 mm VAS).

An average pain score (AVE_VAS) was used by the sponsor to perform an overall assessment of pain associated with the whole procedure. It was defined as:

for EMLA only group: AVE_VAS = mean (VAS1+VAS3);
for 1% Xylocaine group: AVE_VAS = mean (VAS2+VAS3);
for EMLA prior to 1% Xylocaine group: AVE_VAS = mean (VAS1+VAS2+VAS3).

AVE Pain Score median (range)	Treatment Group			P-value
	EMLA only	Xylocaine only	EMLA+Xyl.	
AVE_VAS	10	7.0	0.7	0.0001 (K)
Pairwise Comparisons	10	7.0		0.25 (W)
	10		0.7	0.0001 (W)
		7.0	0.7	0.0001 (W)
Number Of AVE_VAS=0	2 (5.0%)	3 (7.5%)	17 (42.5%)	

Kruskal-Wallis test for multiple comparison was very significant ($p=0.0001$) and median scores were 10, 7.0 and 0.7 for the three groups, respectively. Pairwise comparisons by Wilcoxon test showed that EMLA prior to Xylocaine group had significantly lower pain scores than the other two groups. In addition, the proportion of subjects who had a AVE_VAS=0 was 43% (17) for EMLA prior to Xylocaine group, 8% (3) for Xylocaine only group and 5% (2) for EMLA only group. Therefore, it appeared that the best overall amelioration of pain was provided by EMLA prior to 1% Xylocaine.

This reviewer would like to point out, however, that the use of AVE_VAS for overall evaluation of pain relief in this case can be misleading in the direction of favoring the EMLA prior to Xylocaine group. The following hypothetical example may demonstrate this point. Supposedly, a subject A in the Xylocaine only group had: VAS2=9.0 and VAS3=1.0, and a subject B in the EMLA prior to Xylocaine had: VAS1=1.0, VAS2=9.5 and VAS3=1.5. Then, for subject A, AVE_VAS=(9.0+1.0)/2=5.0, which is a higher average pain score than that of subject B, AVE_VAS=(1.0+9.5+1.5)/3=4.0. But, in fact, subject B experienced not only higher scores in both VAS2 and VAS3, but also an extra pain VAS1.

A possible improvement in the definition of AVE_VAS would be:

for EMLA only group: AVE_VAS = mean (VAS1+0.0+VAS3);
for 1% Xylocaine group: AVE_VAS = mean (0.0+VAS2+VAS3);
for EMLA prior to 1% Xylocaine group: AVE_VAS = mean (VAS1+VAS2+VAS3), same as before.

The new AVE_VAS scores can be obtained by multiplying the old scores by 2/3 for the first two groups and the scores for the third group remain the same. The resulted medians and ranges would be: 6.7 (0-29) for EMLA only group, 4.7 (0-26) for Xylocaine only group, and 0.7 (0-19.3) for EMLA prior to Xylocaine group. The proportion of subjects with AVE_VAS=0 will not change. Therefore, it does not seem to alter the major conclusions made before.

Conclusions

1. EMLA alone does not provide satisfactory pain relief for the surgery.

2. Sponsor's overall evaluation of pain relief using AVE_VAS could be misleading. However, their conclusions seem still valid, i.e., prior use of EMLA followed by Xylocaine may provide the best overall pain amelioration in this surgery procedure among the three choices. The trade-off would be that it prolongs the procedure duration by approximately 15 minutes compared to the Xylocaine only procedure.

3. While the prior use of EMLA may significantly increase the proportion of patients of feeling

"no pain" at the cryotherapy, the reduction of pain for Xylocaine infiltration seems to be more clinically meaningful.

/S/ 4/23/97

Z. Jonathan Ma, Ph.D.
Mathematical Statistician

/S/ 4/23/97

Concur: Thomas Permutt, Ph.D.
Team Leader
Division of Anesthetic, Critical Care
and Addiction Drug Products

/S/ 4/24/97

Concur: Nancy Smith, Ph.D.
Division Director
Division of Biometrics III

Archival: NDA 19-941
cc:
HFD-720/N. Smith
HFD-720 file copy
HFD-720 chron copy
HFD-170/M. Wright
HFD-170/R. Kahn
HFD-170/C. Wright
HFD-170/T. Permutt
HFD-170/J. Ma
HFD-170/division file

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19-941/S-008

ADMINISTRATIVE DOCUMENTS

Division of Anesthetic, Critical Care, and Addiction Drug Products

CONSUMER SAFETY OFFICER LABELING REVIEW NDA 19-941/S-008 Original: December 11, 1997 Addendum: January 23, 1998

Application Number: NDA 19-941
Name of Drug: EMLA (lidocaine 2.5 % and prilocaine 2.5) Cream
Sponsor: Astra USA

Material Reviewed

Submissions Dated: November 5, 1996 accepted February 25, 1997 **(S-008)**
December 3, 1997, received December 4, 1997 **(SNC)**
(electronic submission)

Review: To expedite review of S-008 labeling, a comparative review of the draft labeling that resulted from NDA 19-941/S-007 and S-009, CSO Labeling Review was compared to the labeling submitted on November 5, 1996 (including the electronic submission of this labeling dated, December 3, 1997). S-007, and S-009 contained information regarding the clarification and update of dosing information pertaining to the occlusive dressing dosage form and the disc dosage form.

Since this supplement pertains to the original and new dosage forms, the supplemental labeling revisions applicable to S-008 apply equally to NDA 19-941/S-007, NDA 19-941/S-009, and NDA 20-962.

Specific details to labeling are noted in the attached labeling.

Conclusions: Recommend approval of labeling as stated in attached labeling.

Addendum: S-008 determined to be an efficacy supplement and coded as SE-4, per medical reviewer's comments.

Consumer Safety Officer:
Supervisory Consumer Safety Officer: _____ 01-29-98

/S/

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. /S/
Director,
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

To: File NDA #19-941/SLR-008/Division File
and
Paula Botstein, MD
Director,
Office of Drug Evaluation III
HFD-103

Subject: Approval of EMLA Anesthetic Cream Supplement

This memorandum conveys for the file the basis for the Division's decision for an Approval action to be taken on NDA #19-941 EMLA cream supplements SLR-008.

Background

EMLA Cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%, indicated for local anesthesia of the skin. The application currently under review is a supplement submitted to amend the current indication for adult male genital skin prior to site specific subcutaneous infiltration with lidocaine for the removal of genital warts. The basis for the labeling change is found in a single efficacy study entitled "A Randomized Open-Label Comparative Parallel Group Study to Evaluate the Efficacy and Safety of EMLA Cream and !% Xylocaine Infiltration in Males for Relief of Pain Associated with Removal of Genital Warts by Cryotherapy." This study was reviewed by Curtis Wright, MD Anesthesia Team Leader and Dr. Jonathan Ma, PhD. Because of the disparity between the primary medical reviewer's conclusion and that of the medical team leader an independent review was performed.

The clinical study was an open label three-arm trial in 121 male patients between the ages of 18 and 65 who were scheduled for cryosurgery for the removal of genital warts. Of those patients who entered the study 120 were randomized, to one of three treatments:

- GROUP 1: EMLA Cream only (applied for 15 minutes) prior to surgery
- GROUP 2: 1%Xylocaine infiltration only followed by surgery 10 minutes later
- GROUP 3: EMLA Cream applied for 15 minutes followed by 1% Xylocaine infiltration followed by surgery 10 minutes later.

The study was not blinded. Patients were asked following the surgery to record their pain intensity based on a VAS from 0-100 where "0" was no pain and "100" was worst pain ever. Pain assessments were made immediately following the EMLA application (VAS1), after the Xylocaine injection (VAS2) and after cryosurgery (VAS3). The VAS1 scores were obtained in Groups 1 and 3, VAS 2 scores in group 2 and 3 and VAS3 scores in all groups.

Relief in Pain associated with Injection of Local Anesthetic Comparing 2 Regimens measured on a VAS 0-100				
Efficacy Parameter	**Pain Scores [median (range)] for**			**p-value**
	EMLA	**1% Xylocaine**	**EMLA prior to 1% Xylocaine**	
VAS1	0		0	0.186†
VAS2		9.5	1.0	0.002†
†Wilcoxon Two-sample test				

These results demonstrate that the application of EMLA significantly reduces the pain of injection with Xylocaine (p=.002) where the range of discomfort from injection ranged from (mean 9.5) without the application of EMLA and ranges from with the application of EMLA prior to injection.

The sponsor agrees that the results demonstrate that the application of EMLA alone did not reduce the pain of cryosurgery to a bearable level.

Relief in Pain associated with Cryosurgery Comparing 3 Regimens measured on a VAS 0-100				
Efficacy Parameter	**Pain Scores [median (range)] for**			**p-value**
	EMLA	**1% Xylocaine**	**EMLA prior to 1% Xylocaine**	
VAS3	17	1.5	0	0.0001†
Pairwise comparisons for VAS3	17	1.5		0.0001‡
	17		0	0.0001‡
		1.5	0	0.005‡

†Kruskal-Wallis ‡Wilcoxon

It further demonstrates that there is a significant reduction in the pain associated with cryosurgery with Xylocaine. The addition of EMLA prior to surgery produces a statistically significant difference between the two groups but arguably the clinical difference between a VAS score of 0 and 1.5 is negligible.

One could readily conclude that the meaningful effect of EMLA is in the relief of pain associated with the injection of Xylocaine. I concur with the Dr. Ma's conclusions that EMLA alone does not produce satisfactory pain relief for cryosurgery and that the reduction of pain associated with Xylocaine injection in groups 2 and 3 is clinically meaningful.

However, when one looks at the percentage of patients who reported no pain at any time during with the procedure (including the pain of local infiltration) 17 (43.5%) of patients who received EMLA and Xylocaine reported no pain, while only 2 (5%) of patents in the EMLA group and 3 (7.5%) in the Xylocaine group reported no pain during any part of the procedure including the infiltration of Xylocaine. Because the

first analysis described was able to better separate the effects of the components of the various procedures, it is considered more valid.

There were no prospective efficacy variables described in the clinical protocol of this study.

Turning to pharmacokinetics, the second part of this study was performed in order to characterize the pharmacokinetics profile of EMLA cream. In this portion of the study EMLA was applied to male genital skin in 20 patients in doses ranging from g for minutes. Plasma concentrations of lidocaine and prilocaine were obtained and the pharmacokinetics profile of EMLA cream was developed.

Pharmacokinetics Variables for Lidocaine		
Variable	**Plasma Lidocaine following**	
	EMLA topical	**1 % Xylocaine (10 mg IV)**
AUC_{0-t} (mg/mL*h)	19.1±11.9	163.4±95
$AUC_{0-\infty}$ (mg/mL*h)	32.4±14.5	196.6±108
C_{max}	6.6±3.8	714±1713
t_{max}	1.59±.78	0.05±0.05
$T_{1/2}$	3.5±1.1	2.2±.5

Pharmacokinetics Variables for Prilocaine		
Variable	**Plasma Prilocaine following**	
	EMLA topical	**Clinatest Plain (10 mg IV)**
AUC_{0-t} (mg/mL*h)	5.5±5.7	109.8.±180.2
$AUC_{0-\infty}$ (mg/mL*h)	12.9± 5.4	119.8±180.5
C_{max}	3.9±1.5	2401±7648
t_{max}	1.39±.78	0.06±0.05
$T_{1/2}$	N/A	2.0±.2

These results of this part of the study show that systemic exposure to lidocaine /prilocaine from EMLA used for the relief of pain associated with lidocaine injection for the purpose of producing local anesthesia for removal of genital warts is consistently low.

The sponsor's recommended labeling cannot be supported fully by the data provided. The recommended labeling is attached to this memo with language that is more conservative and in keeping with the findings of the study referenced here.

APPEARS THIS WAY
ON ORIGINAL

Debarment Certification

This certifies that Astra USA, Inc. has not used in any capacity any person identified by the United States Food and Drug Administration on the recent Debarment List.

Further, we certify that Astra USA, Inc. will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

The following is a list of all relevant convictions (for which a person can be debarred) as described in section 306 (a) and (b). The list covers the past five (5) years for persons employed and/or affiliated with Astra USA, Inc. (including contractors) and responsible for the development of data and information to support approval of NDA 19-941 S-008 (SE4) for EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%).

Person	Date of Conviction	Charge
None	None	None

Dennis J. Buccéri
Vice President
Regulatory Affairs

1/28/98
Date

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Person	Date of Conviction	Charge
None	None	None

Dennis J. Bucceri
Vice President
Regulatory Affairs

1/28/98
Date

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

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 19-941 Supplement # 008 SE4

HFD-170 Trade and generic names/dosage form: EMLA Cream(lidocaine 2.5% and prilocaine 2.5%
Action: AP

Applicant Astra USA, Inc Therapeutic Class 3S

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 is for pre-procedural application of EMLA Cream to adult genital skin prior to site-specific subcutaneous infiltration with lidocaine for the removal of genital warts. (For supplements, answer the following questions in relation to the proposed indication.)

___ 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.

/S/ _____ 1/28/98

Signature of Preparer and Title/Date Project Manager/CSO/Date

cc: Orig NDA/PLA/PMA # 19-941/S-008
HFD-170 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (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 the time of the last action. (revised 1/28/98)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19-941/S-008

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
Regulatory Affairs

MAILING ADDRESS:
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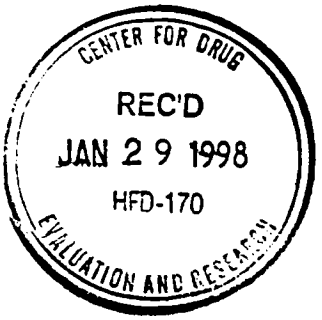
ASTRA®
Astra USA

NDA 19-941/S-008 (SE4)
EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%)

RESPONSE TO REQUEST FOR INFORMATION

January 28, 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 a January 27, 1998 telephone conversation with Mr. Ken Nolan, Project Manager. During that conversation, Mr. Nolan explained that supplement S-008 had been reclassified from an SLR (labeling revision) to and SE (efficacy) supplement. Therefore, a debarment certification, patent information, and request for exclusivity were required.

Enclosed please find a debarment certification, patent information, and a request for exclusivity for NDA 19-941/S-008 (SE4). Astra USA believes that the inclusion of this information will make S-008 complete, and will allow the Agency to move forward with approval process for all pending supplements to NDA 19-941: S-004, S-007, S-008, and S-009.

If you have any questions regarding this correspondence, please feel free to contact me at (508) 836-8488, or Paul J. Damiani, Ph.D., at (508) 366-1100, ext. 4772.

Sincerely,

Brian A. Green

Brian A. Green
Regulatory Affairs Specialist
Regulatory Affairs

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6810105-Cable/Astrapharm

DUPLICATE

NDA NO. 19-941 REF. NO. 5-008

NDA SUPPL FOR SLR

ASTRA®
Astra USA

CENTER FOR DRUG
REC'D
NOV 07 1996
HFD-170
EVALUATION AND RESEARCH

NDA 19-941
EMLA® Cream (lidocaine 2.5 % and prilocaine 2.5%)

SUPPLEMENTAL APPLICATION

November 5, 1996

Curtis Wright, M.D., Acting Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
ODE II, CDER, FDA
HFD-170, Room 9B-45
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Wright:

Reference is made to our approved New Drug Application for EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%), NDA 19-941.

Enclosed please find a supplemental application, which provides for a revision to our labeling to specify a shorter duration of application when EMLA Cream is applied to male genital skin.

In support of this change, the following documents are enclosed:

A mock-up copy of our package insert indicating the changes we are proposing.

Final report for Protocol 93-EML-18, entitled, "A Randomized, Open-Label, Comparative, Parallel Group Study to Evaluate the Efficacy and Safety of EMLA® Cream and 1% Xylocaine® Infiltration in Males for Relief of Pain Associated with the Removal of Genital Warts by Cryotherapy."

The documents are organized according to the attached table of contents. If you should have any questions, please contact me at (508) 366-1100, Extension 4772.

Sincerely,

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

NAI: No clinical data in this submission 12-3-96

PJD/bag

ORIGINAL

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