CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-941 / S-012

Trade Name: EMLA Cream
Generic Name: Lidocaine 2.5% and prilocaine 2.5%
Sponsor: AstraZeneca LP
Approval Date: April 20, 2000
**APPLICATION NUMBER:**

19-941 / S-012

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NDA 19-941/S-012
NDA 20-962/S-001

AstraZeneca LP
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

Attention: Lisa DeLuca, Ph.D.
            Regulatory Liaison Director

Dear Dr. DeLuca:

Please refer to your supplemental new drug applications dated August 27, 1999, received August 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%), and EMLA® Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5%) Topical Adhesive System.

We acknowledge receipt of your submissions dated October 12, 1999.

These supplemental new drug applications provide for the use of EMLA® Cream and EMLA® Anesthetic Disc Topical Adhesive System for topical dermal analgesia in geriatric patients.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

1. The following statement should be placed in the section entitled CLINICAL PHARMACOLOGY.

   During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients.

2. The Geriatric Use sub-section should be modified as follows.

   Of the total number of patients in clinical studies of EMLA, 180 were 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
Archival NDAs 19-941, 20-962
HFD-170/Div. Files
HFD-170/L.Governale
HFD-170/H.Blatt, P.Maturu, C.Schumaker
HFD-170/A.D'Sa, B.Rappaport, R.Uppoor, C.McCormick
HFD-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
DISTRICT OFFICE

Drafted by: Ig/April 19, 2000
Initialed by: Blatt/4-20-00, Kim/4-20-00, Uppoor/4-20-00, Rappaport/4-20-00
final: Rappaport/4-20-00
filename: 19941.S012(AstraZeneca)AP022300.doc

APPROVAL (AP)
younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of EMLA are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). (See CLINICAL PHARMACOLOGY).

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted August 27, 1999). These revisions are terms of the approval of these applications.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-941/S-012 and 20-962/S-001." Approval of these submissions by FDA is not required before the labeling is used.

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

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857
EMLA CREAM (lidocaine 2.5% and prilocaine 2.5%)

DESCRIPTION

EMLA cream is anesthetic ointment containing 2.5% lidocaine and 2.5% prilocaine. It is a white, opaque, emollient-based anesthetic ointment intended for the topical anesthesia of the skin prior to small surgical procedures. The cream is supplied as a single-use, pre-packaged desiccated sachet. Each sachet contains 5.6 g of cream, which is equivalent to 0.14 g of lidocaine and 0.14 g of prilocaine.

CLINICAL PHARMACOLOGY

Mechanism of Action:

EMLA cream contains lidocaine and prilocaine, both local anesthetics of the amide type. Lidocaine and prilocaine are rapidly absorbed from the skin and the concentration of lidocaine is achieved in the vascular compartment, while prilocaine is more slowly absorbed. Once the anesthetic is absorbed, it is metabolized in the body, with lidocaine being rapidly metabolized to a variety of inactive metabolites and prilocaine being metabolized to a lesser extent.

Indications:

EMLA cream is indicated for the temporary topical anesthesia of the skin of the hands, feet, and perineum in infants, children, and adults for minor surgical procedures and minor pain associated with injections, catheterizations, and childhood immunizations.

Contraindications:

EMLA cream is contraindicated in patients with a history of anaphylactic reactions to any component of the formulation. It is also contraindicated in patients with a history of hypersensitivity to amide-type local anesthetics.

Precautions:

EMLA cream should be used with caution in patients with pre-existing conditions that may affect the absorption or metabolism of lidocaine or prilocaine. These include severe hepatic or renal insufficiency, and patients with a history of seizures or other neurological disorders.

Adverse Reactions:

The most common adverse reactions reported with the use of EMMA include skin irritation, pruritus, and burning sensation. Other rare adverse reactions include contact dermatitis, allergic contact dermatitis, and anaphylactic reactions.

Dosage and Administration:

EMLA cream is applied to the skin for a minimum of 30 minutes prior to the procedure. The area to be anesthetized should be cleaned with an antiseptic solution and allowed to dry before the application of EMLA cream. The cream should be applied to a thin layer to the skin and left in place for 30 minutes. After the procedure, the anesthesia is interrupted by rinsing the area with water.

Instruct the patient to use a clean, dry cloth after the procedure.

TABLE 1

Table showing the results of various studies comparing EMMA to other local anesthetics

TABLE 2

Table showing the maximum recommended dose of EMMA for different age groups

INSTRUCTIONS FOR APPLICATION

1. In infants, apply 0.5 g of cream (10 x 5 g packets, 5 x 10 g packets, 25 x 10 g packets) (approx. 2.5 g of cream) in a thin layer to the site of the procedure. For pediatric patients, apply 0.5 g of cream in a thin layer to the site of the procedure. For adult patients, apply 1.0 g of cream in a thin layer to the site of the procedure. The cream should be applied to the skin in a thin layer and left in place for 30 minutes. After the procedure, the anesthetic is interrupted by rinsing the area with water.

2. Take an occlusive dressing (gauze, sterile gauze, sterile gauze, sterile gauze, sterile gauze) and cover the end of the treatment.

3. Peel the paper cover from the topical anesthetic.
DNA Damage in the renal tubular system, however, is not determined. DNA should not be used in any clinical situation in which it could be associated with a reduction in the number of viable cells or in tissues at risk for degeneration.

Measurement of Neutrophil DNA Damage

Neutrophils are white blood cells that circulate in the blood and are released into the tissue when an infection occurs. When neutrophils are exposed to DNA-damaging agents, such as ionizing radiation or certain drugs, they undergo a process called apoptosis, or programmed cell death. DNA damage in neutrophils can be measured by quantifying the amount of DNA that is released into the extracellular space.

To measure neutrophil DNA damage, a culture of neutrophils is treated with the agent of interest and then incubated for a specified period of time. The cells are then harvested and lysed, and the DNA is isolated. The amount of DNA that is released into the extracellular space is quantified using a variety of methods, such as the Comet Assay, DNA Fragmentation Assay, or Flow Cytometry.

This method is important for understanding the mechanisms of DNA damage and repair in neutrophils, as well as for evaluating the potential toxic effects of drugs or radiation on the immune system.

Neutrophil DNA Damage in Patients with Neutrophil Disorders

Neutrophil DNA damage has been measured in patients with various neutrophil disorders, such as Neutropenic Enterocolitis, Acute Myeloid Leukemia, and Chronic Neutrophilic Leukemia. In these patients, DNA damage has been found to be increased, which may contribute to the increased susceptibility to infection and the development of sepsis.

Conclusions

In conclusion, the measurement of neutrophil DNA damage is a valuable tool for understanding the mechanisms of DNA damage and repair in neutrophils, as well as for evaluating the potential toxic effects of drugs or radiation on the immune system. Further studies are needed to determine the clinical relevance of these findings.

References


Additional Information

For more information on the measurement of neutrophil DNA damage, please visit the following websites:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357638/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000031/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2926797/


DOSAGE AND ADMINISTRATION
A. Adults

EMLA Cream and Infiltration
- EMLA Cream is applied to intact skin and covered with an occlusive dressing or adhesive bandage. EMLA Nerve block is one of the most common techniques for EMLA Cr.
- Infiltration is the most appropriate technique for EMLA Cr.

B. Children

EMLA Cream is not recommended for use in children under the age of 3 months. EMLA Cr. is not recommended for use in children under the age of 3 months.

C. EMLA Nerve block

EMLA Cr. is a non-steroidal anti-inflammatory drug (NSAID). It is a topical anesthetic cream that is used to numb the skin before a surgical procedure. It is available as a cream or spray and is applied to the skin for a period of time before the procedure. EMLA Cr. can be used to numb the skin for a variety of procedures, including circumcision, dermabrasion, and Mohs surgery.

CONTRAINDICATIONS
EMLA Cr. is contraindicated in patients with a history of allergy to local anesthetic agents (e.g., procaine, lidocaine, mepivacaine, prilocaine), patients with a history of hypersensitivity to any of the excipients in the formulation, or patients with a history of allergy to local anesthetic agents. EMLA Cr. is also contraindicated in patients with a history of allergy to non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, or aspirin.

WARNINGS
EMLA Cr. should be used with caution in patients with a history of bleeding disorders, or in patients currently taking anticoagulants or aspirin, as EMLA Cr. may cause bleeding at the site of injection.

ADVERSE REACTIONS
EMLA Cr. may cause mild to moderate skin irritation, including erythema, pruritus, and burning, which may persist for up to 7 days after application. EMLA Cr. may also cause systemic adverse effects, including headache, dizziness, and nausea.

INFORMATION FOR PATIENTS
EMLA Cr. is a topical anesthetic cream that is applied to the skin before a surgical procedure. It is available as a cream or spray and is applied to the skin for a period of time before the procedure. EMLA Cr. can be used to numb the skin for a variety of procedures, including circumcision, dermabrasion, and Mohs surgery.

HOW SUPPLIED
EMLA Cr. is supplied in the following strengths:
- EMLA 1-0.5% cream (10 g)
- EMLA 2-0.5% cream (10 g)
- EMLA 2-1% cream (10 g)
- EMLA 2-0.5% spray (5 mL)

INFORMATION FOR PATIENTS
- EMLA Cr. is a topical anesthetic cream that is applied to the skin before a surgical procedure. It is available as a cream or spray and is applied to the skin for a period of time before the procedure. EMLA Cr. can be used to numb the skin for a variety of procedures, including circumcision, dermabrasion, and Mohs surgery.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-941 / S-012

MEDICAL REVIEW
NDA 19-941/Geriatric Supplement SLR-012

Sponsor: ASTRA Pharmaceuticals, L.P.
Name: EMLA Cream (lidocaine 2.5% and prilocaine 2.5%)
Type of Submission: Geriatric Labeling Supplement
Proposed Indication: Topical analgesia/anesthesia.
Reviewer: Harold Blatt, D.D.S.
Team Leader: Bob Rappaport, M.D.
Letter Date by Sponsor: August 27, 1999
Date Received by CDER: August 27, 1999
Date Received by Reviewer: December 14, 1999
Date Review Completed: February 1, 2000
CSO: Laura Governale

Background:

This submission is a labeling supplement for “Geriatric Use” of the EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) indicated for topical anesthesia/analgesia indicated for topical anesthesia/analgesia.

Abstract:
The sponsor refers to 21 CFR 201.57(f)(10)(ii)(B) and states that:

- Clinical studies do contain a sufficient number of geriatric patients to determine whether elderly patients respond differently from younger subjects
- Pharmacokinetic documentation does not indicate any dose reduction is necessary in geriatric patients from a safety point of view

Sponsor’s Data to Support Geriatric Use Labeling:
The sponsor submitted geriatric additions to the label based on their ISE and ISS, pharmacokinetic studies, post marketing surveillance, and a medical literature review of databases. They found no reports of differences in clinical experience for those subjects compared to younger subjects [Vol. 1.1, p.197.]

ISE:

In the sponsor’s ISE, the results of 6 studies were pooled. Of these two were open, randomized, parallel, active controlled studies (86EM20, and 051-27), one was a double blind, randomized, parallel, dose controlled study (85EM14), and 3 were open, single center, uncontrolled studies (800034, 82P033, and 83P030).

On the following page is a summary table (Table 1) of demographic data in all studies included in the sponsor’s ISE by age group:
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age group</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMLA</td>
<td>&lt; 65</td>
<td>38.0</td>
<td>14</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>70.0</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>&gt;= 75</td>
<td>81.0</td>
<td>75</td>
<td>96</td>
</tr>
<tr>
<td>Missing age</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Act control</td>
<td>&lt; 65</td>
<td>32.0</td>
<td>17</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>67.0</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>&gt;= 75</td>
<td>81.0</td>
<td>76</td>
<td>87</td>
</tr>
</tbody>
</table>

[Vol. 1.1, p.120].

The sponsor analyzed the open active controlled trials and found no statistically significant difference in VAS pain scores from the cutting of a split-skin graft between geriatric patients treated with EMLA or Xylocaine infiltration, (p = 0.256). [Vol. 1.1, p.124] Analysis of the dose controlled study showed that both geriatric and non-geriatric patient groups felt no or only slight pain during the cutting of the split-skin graft. [Vol. 1.1, p.126]. The statistical analysis performed the three uncontrolled studies showed no statistically significant difference in VRS pain scores from the cutting of a split-skin graft between EMLA-treated geriatric and non-geriatric patients (p = 0.196). [Vol. 1.1, p.129].

Based on the 6 studies in their ISE, the sponsor concluded that efficacy in geriatric patients was not statistically significantly different from the efficacy in non-geriatric patients. [Vol.1.1, p.132.]

**ISS:**

The ISS summarizes 20 studies on intact skin (including the 6 studies listed in the sponsor's ISE). Studies were divided into three groups. One group included studies on split skin grafting, a second group of intact skin studies in geriatric and non-geriatric patients with electronic data available, and a third group of intact skin studies in just geriatric patients with electronic data available. These studies are listed in the table 2 on the next page:
<table>
<thead>
<tr>
<th>Category</th>
<th>Blinding</th>
<th># of studies</th>
<th>Study codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Split-skin grafting studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active-controlled</td>
<td>Open, randomized</td>
<td>2</td>
<td>86EM20, 051-27</td>
</tr>
<tr>
<td>Dose-controlled</td>
<td>Double-blind</td>
<td>1</td>
<td>85EM14</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>Open</td>
<td>3</td>
<td>800034, 82P033, 83P030</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Other intact skin studies where data from both geriatric and non-geriatric patients are available in electronic format**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Blinding</th>
<th># of studies</th>
<th>Study codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled single-dose parallel</td>
<td>Double-blind</td>
<td>3</td>
<td>82P003, 6220(051-21), 051-46</td>
</tr>
<tr>
<td>Placebo-controlled repeated-dose parallel</td>
<td>Double-blind</td>
<td>1</td>
<td>91EM15</td>
</tr>
<tr>
<td>EMLA Cream vs EMLA Anesthetic Disc parallel</td>
<td>Open, randomized</td>
<td>2</td>
<td>051-28, 052-01</td>
</tr>
<tr>
<td>EMLA Cream vs EMLA Anesthetic Disc vs placebo crossover</td>
<td>Open, randomized</td>
<td>1</td>
<td>051-36</td>
</tr>
<tr>
<td>Uncontrolled repeated-dose</td>
<td>Open</td>
<td>1</td>
<td>051-20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Other intact skin single-dose studies where data from geriatric patients only are available in electronic format**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Blinding</th>
<th># of studies</th>
<th>Study codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled parallel</td>
<td>Double-blind</td>
<td>1</td>
<td>3-EML-03A</td>
</tr>
<tr>
<td>Placebo-controlled crossover</td>
<td>Double-blind</td>
<td>1</td>
<td>S80201-405-007*</td>
</tr>
<tr>
<td>Active-controlled, crossover</td>
<td>Open, randomized</td>
<td>1</td>
<td>85EM05</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>Open</td>
<td>3</td>
<td>3-EML-01, 84EM01, 87EM11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Grand total**                          |                           | 20           |                      |

Table 2. [Vol. 1.1, p.147.]
From the ISS table above it was found that 5 studies appear to be adequate and well-controlled (randomized, double-blind, and either placebo or dose controlled) for this indication. These studies contained patients over 65 as follows: Study 82P003 had 1 patient, 6220(051-21) had no patients, 051-46 had 12 patients, 3-EML-03A had 1 patient, and S80201-405-007 had 29 patients. (Study 85EM14 was a dose controlled trial and not adequate and well controlled [AWC] and Study 91EM15 was for a different indication.) This totals up to 33 patients over 65. In addition, the sponsor did not provide a breakout of these patients who were 75 or older. However, the total number of patients exposed to EMLA from all the pooled trials is 318. Of this number 138 are 75 or older. These numbers are sufficient to meet the ICH guidelines.
### Number of Patients exposed to EMLA in all Studies in the ISS

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>All split skin grafting studies (Studies 800034, 82P033, 83P030, 85EM14, 86EM20, and 051-27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>38.0</td>
<td>14</td>
<td>64</td>
</tr>
<tr>
<td>65-74</td>
<td>70.0</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>≥75</td>
<td>81.0</td>
<td>75</td>
<td>96</td>
</tr>
<tr>
<td><strong>Other controlled and uncontrolled intact skin studies available in electronic format (Studies 82P003, 91EM15, 051-21, 051-28, 051-46, 052-01, 051-20, and 051-36)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>41.0</td>
<td>16.0</td>
<td>64.0</td>
</tr>
<tr>
<td>65-74</td>
<td>70.0</td>
<td>65.0</td>
<td>74.0</td>
</tr>
<tr>
<td>≥75</td>
<td>79.0</td>
<td>75.0</td>
<td>90.0</td>
</tr>
<tr>
<td><strong>Other intact skin studies (only patients ≥65) (Studies 85EM05, S80201, 3EML01, 3EML03A, 84EM01, 87EM11)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>65-74</td>
<td>69.0</td>
<td>65.0</td>
<td>74.0</td>
</tr>
<tr>
<td>≥75</td>
<td>78.0</td>
<td>76.0</td>
<td>88.0</td>
</tr>
</tbody>
</table>

Table 3. [Table based on Tables 2, 6, and 7 Vol. 1.1, pp. 153, 155-156.]

Note: The numbers in bold in the Total (n) column on the right side of the table above represent the source of the number of patients exposed to EMLA that are referred to in the sponsor’s labeling. 182 (100+82) geriatric patients were exposed to EMLA in the split skin grafting trials, and 136 (53+29+45+9) geriatric patients were exposed to EMLA in all other trials included in this ISS. The total number of patients exposed comes to 318 (136+182).
Application area (cm²) in dose controlled and uncontrolled split-skin grafting studies

<table>
<thead>
<tr>
<th>Uncontrolled</th>
<th>Study Number</th>
<th>n</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>Min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>800034</td>
<td>92</td>
<td>164</td>
<td>95.0</td>
<td>287.0</td>
<td>24.0</td>
<td>1500.0</td>
</tr>
<tr>
<td></td>
<td>82P033</td>
<td>35</td>
<td>150</td>
<td>77.0</td>
<td>200.0</td>
<td>16.0</td>
<td>348.5</td>
</tr>
<tr>
<td></td>
<td>83P030</td>
<td>16</td>
<td>200</td>
<td>150.0</td>
<td>250.0</td>
<td>75.0</td>
<td>375.0</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>800034</td>
<td>54</td>
<td>130</td>
<td>88.0</td>
<td>200.0</td>
<td>25.0</td>
<td>500.0*</td>
</tr>
<tr>
<td></td>
<td>82P033</td>
<td>56</td>
<td>130.0</td>
<td>104.5</td>
<td>186.8</td>
<td>42.0</td>
<td>420.0</td>
</tr>
<tr>
<td></td>
<td>83P030</td>
<td>11</td>
<td>150.0</td>
<td>150.0</td>
<td>180.0*</td>
<td>80.0</td>
<td>200.0</td>
</tr>
</tbody>
</table>

Table 4. [Based on sponsor’s table 13, Vol. 1.1, p.161.]
Note: 25% of geriatric patients had an application area of more than 180 cm². The maximum application area was 500 cm². (See bolded numbers with asterisks). However, this was only for the 121 patients in the dose controlled and uncontrolled split skin grafting studies.

Application time (minutes) in dose-controlled and uncontrolled, split-skin grafting studies

<table>
<thead>
<tr>
<th>Dose-controlled/ uncontrolled</th>
<th>Study Number</th>
<th>n</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>800034</td>
<td>92</td>
<td>165</td>
<td>150</td>
<td>220</td>
<td>110</td>
<td>460</td>
</tr>
<tr>
<td></td>
<td>82P033</td>
<td>33</td>
<td>190</td>
<td>155</td>
<td>255</td>
<td>0</td>
<td>350</td>
</tr>
<tr>
<td></td>
<td>83P030</td>
<td>16</td>
<td>150</td>
<td>122.5</td>
<td>150</td>
<td>90</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>85EM14</td>
<td>45</td>
<td>150</td>
<td>135</td>
<td>210</td>
<td>75</td>
<td>290</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td>165</td>
<td>145</td>
<td>220</td>
<td>0</td>
<td>460</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>800034</td>
<td>54</td>
<td>177.5</td>
<td>150</td>
<td>215</td>
<td>120</td>
<td>460</td>
</tr>
<tr>
<td></td>
<td>82P033</td>
<td>54</td>
<td>173.5</td>
<td>140</td>
<td>245</td>
<td>77</td>
<td>495*</td>
</tr>
<tr>
<td></td>
<td>83P030</td>
<td>11</td>
<td>150</td>
<td>135</td>
<td>165*</td>
<td>120</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>85EM14</td>
<td>40</td>
<td>165</td>
<td>127.5</td>
<td>192.5</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>165</td>
<td>142</td>
<td>215</td>
<td>75</td>
<td>495*</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. [Based on sponsor’s table, Vol. 1.1, p.179.]
Note: 25% of geriatric patients had an application time of at least 165 minutes up to a maximum in excess of 8 hours (up to 495 minutes). See bolded numbers with asterisks in the table above.

Although the sponsor provides information on application area and application time (as shown above) for use in the label, I believe that for the sake of clarity and standardization, language based on that provided in 21 CFR 201.57(f)(10)(ii)(B) would be preferable.

This reviewer looked at the frequency and severity of adverse events in intact skin trials by age group and found the percentages were similar for those over 65 and those 64 and under. Mild application site disorders were 71.9% for those 64 and under and 70.7% for those over 65. They were 4.7% for 64 and under and 3.7% for those over 65 for moderate application site disorders. Skin and appendages were 1.3% for those 64 and under and 1.2% for those over 65. [Vol. 1.1, p.185.]
REVIEW OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Deaths
The only death reported occurred in the placebo-controlled crossover study S80201. A 65 year old woman received about 5 g EMLA to the dorsum of one hand prior to intravenous cannulation for surgery. During the surgery she had a myocardial infarction and died eight hours after EMLA application. The MI was not suspected of having any relationship with the drug. The dose of EMLA was so small and there should be very little percutaneous absorption (systemic plasma levels of lidocaine and prilocaine are not detectable after a dose of 2.5 g EMLA in children.)

Other serious adverse events
There were no other serious adverse events reported in these studies.

Other significant adverse events
Only one significant adverse event was reported in the split-skin grafting study 82P033. A 90-year-old male with prediagnosed arrhythmia suffered a bradycardia. An area of 104 cm$^2$ on his upper arm had been covered with EMLA for 120 minutes. During the operation his pulse rate was 40-50 beats per minute, which was interpreted as a bradycardia. (Pulse was not checked prior to surgery). He did not experience any discomfort during the operation. The patient had been taking digoxin for ten years for arrhythmia. ECG verified the arrhythmia (atrial fibrillation). The patient left hospital without any sequelae. One month later he was reoperated on with EMLA anesthesia without adverse events. The bradycardia is not suspected of having had any connection with the application of EMLA cream.

Discontinuations due to adverse events
In study S80201 a 68-year-old female patient had extreme shortness of breath before any EMLA had been applied. After application, her anxiety and dyspnea increased, and her procedure was cancelled by the anesthesiologist. The sponsor state that her diagnosis was critical aortic stenosis, with a 70-minute gradient across the aortic valve, an aortic valve area of 0.4 cm$^2$ and a pulmonary capillary wedge pressure of 28. She was operated on two days later, having exactly the same lab values and symptoms, and this time had no complications during the procedure. The shortness of breath recorded in the CRF was not considered drug related.

In the repeated-dose study 91EM15 an EMLA-treated 20 year old female patient withdrew from the study on day 3 due to mild maceration of the skin at the area of the plastic occlusion. The AE lasted one hour and the patient was completely recovered.

Other safety considerations
EMLA was first introduced in 1984. Most adverse events (AEs) reported were application site reactions. A clinically significant increase in methemoglobin has been observed in a few children; but were thought to be due to concomitant therapy with a
methemoglobin-inducing agent and use in a pre-term infant (where the drug is contraindicated), or due to overdosing.

There has been no case of methemoglobinemia reported in adults. [Vol. 1.1, pp.170-172.]

**Pharmacokinetic Studies:**

The sponsor has provided 4 pharmacokinetic studies as follows: Table 6. [Vol. 1.1, p.27]

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose / Route of administration</th>
<th>&lt; 65 years</th>
<th>≥ 65 ≤ 74 years</th>
<th>≥ 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nation (1)</td>
<td>50mg lidocaine IV</td>
<td>7</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Abernethy (2)</td>
<td>25mg lidocaine IV</td>
<td>24</td>
<td>13³</td>
<td>-</td>
</tr>
<tr>
<td>Cusack (3)</td>
<td>250 mg lidocaine PO and 50 mg lidocaine IV</td>
<td>6</td>
<td>6¹</td>
<td>-</td>
</tr>
<tr>
<td>Olsén (4)</td>
<td>EMLA® Cream 5%</td>
<td>65</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>

¹ There is no information on the age of the individual subject.

1. Nation RL, Triggs EJ. Lidocaine kinetics in cardiac patients and aged subjects. British Journal of Clinical Pharmacology 1977; 4: 439-48. Six elderly (> 60 years of age) long-term stay male residents and four young healthy males were studied. Each subject received 50-mg lidocaine HCl (Xylocaine 0.5% Plain, Astra) injected over 1 min via an antecubital vein. The elimination half-life (t₁/₂) of lidocaine was prolonged in the aged subjects (139.60 ± 64.09 min) compared with the young individuals (80.58 ± 9.40 min), whereas the plasma clearance (CL) was similar in both groups.

2. Abernethy DR, Greenblatt DJ. Impairment of lidocaine clearance in elderly male subjects. Journal of Cardiovascular Pharmacology 1983; 5: 1093-6. Six elderly male (aged 65-75), seven elderly female (aged 64-88), 15 young male (aged 22-38), and nine young female (aged 25-37) volunteers were studied. All subjects received a single intravenous dose of 25mg lidocaine HCl over 30 seconds. T₁/₂ was prolonged in elderly male (2.7 ± 0.21 h) as compared with young male subjects (1.66 ± 0.09 h), which was the result of a decrease in CL (12.9 ± 2.0 versus 19.8±1.5 ml/min/kg). No difference in t₁/₂ was noted among female subjects.

3. Cusack B, O'Malley K, Lavan J, Noel J, Kelly JG. Protein binding and disposition of lignocaine in the elderly. European Journal of Clinical Pharmacology 1985; 29: 232-9. This study gave single doses of lidocaine 250 mg orally (lidocaine HCl capsules, Astra Pharmaceuticals) and 50 mg intravenously over 5 minutes (Xylocaine 2%, Astra Pharmaceuticals) in random order to six young and six elderly nonsmokers. After intravenous administration the plasma-concentration time curves were similar in both groups for the first two hours but then a slower rate of decline occurred in the elderly subjects. However, although the elimination half-life in the geriatric group was 30% longer than in the young volunteers, there was no difference in the volume of distribution.
or clearance between the groups. The bioavailability of lidocaine was considerably
greater in the older subjects. Binding was higher in the elderly subjects

The findings from three studies on the IV pharmacokinetics of lidocaine in elderly
subjects (1, 2, and 3) provide mixed results. In all studies the elimination half-life was
statistically significantly longer in elderly than in younger subjects with a 70 % (1), 60 %
(2) and 30 % (3) prolongation of the mean elimination half-life, respectively. However, in
the second study the half-life was longer only in the male subjects. The longer
elimination half-life was due to a larger volume of distribution in the elderly in the first
study (1) and to a lower clearance in elderly males in the second study (2), whereas in the
third study (3) no significant age-related differences were observed in either volume of
distribution or clearance.

4. Ohlsen L, Englesson S, Evers H. An anesthetic Lidocaine/prilocaine cream
(EMLA®) for epicutaneous application tested for cutting split skin grafts. Scand J Plast
Reconstr Surg 1985; 19:201-9. Ohlsen et al. (4) studied the plasma levels of lidocaine
and prilocaine following application of EMLA® Cream to the skin for the cutting of split-
skin grafts in 107 patients (20 patients between 65-74, 22 patients 75 or older, and 65
patients under 65).

Following application of EMLA® Cream to intact skin areas of up to 375 cm² in geriatric
patients, mean lidocaine and prilocaine plasma levels were 137 ng/ml and 139 ng/ml,
respectively in patients 65-74 years of age (n=20), and 54 ng/ml and 26 ng/ml,
respectively in patients >75 (n=22). There was no difference in lidocaine plasma levels
on removal or 3 hours after removal of the cream, whereas prilocaine plasma levels were
lower on removal of the cream in patients >75 compared to patients <65 years of age
(n=65). Consequently, there are no indications on higher systemic plasma levels of
lidocaine and prilocaine following application of EMLA® Cream to intact skin in
geriatric patients than in non-geriatric patients.

[Vol. 1.1, pp. 27, 29, 31,33.]

Please see PK review for more details regarding these studies.

Post marketing surveillance

The sponsor’s review of their post marketing surveillance revealed that, as of 8-6-99, a
total of 70 patients 65 or older, 23 of which were 75-90 were included in the safety report
database. The sponsor, however, did not provide post marketing data on patients under 65
for comparison. [Vol. 1.1, p.192.]

Other Data:

The sponsor’s review of medical literature databases (Medline, Embase, ADIS, LMS
Alerts and Delphi Medlit found no reports of differences in clinical experience for those
subjects compared to younger subjects [Vol. 1.1, p.197.] This reviewer conducted a
Pubmed search from October of 1999 to December of 1983 that did not reveal sources specific to dosing in the elderly that were not submitted by the sponsor.

**Discussion:**

Because the overall number of patients exposed to EMLA was 318, the geriatric information available for this product is consistent with 21 CFR 201.57(f)(10)(ii)(B). Namely, that clinical studies do contain a sufficient number of geriatric patients to determine whether elderly patients respond differently from younger subjects but no such differences were observed. This reviewer would prefer that wording be based on that contained in 21 CFR 201.57(f)(10)(ii)(B) are used.

Although approximately 90% lidocaine metabolites and < 10% of lidocaine parent drug administered are excreted through the kidney, systemic exposure of lidocaine prilocaine from EMLA cream is not great. It should also be noted that the metabolite is inactive. Therefore, according to Dr. Shinja Kim, Biopharm Reviewer, and Dr. Ramana Uppoor Biopharm Team Leader, language regarding the standard renal precaution can be omitted. This reviewer concurs with their opinion. For a more detailed discussion of PK issues, see Biopharm review.

Because pharmacokinetic studies were conducted in the elderly, according to 21 CFR 201.57(f)(10)(iii)(A), they should be described in the “Clinical Pharmacology” section of the labeling as well as the “Geriatric Use” subsection.
WITHHOLD ___ PAGE(S)

Draft Labeling
APPLICATION NUMBER:

19-941 / S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Division of Anesthetic, Critical Care, and Addiction Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number:  
NDA 19-941/S-012  
NDA 20-962/S-001

Name of Drug:  
EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%), and  
EMLA® Anesthetic Disc (lidocaine 2.5% and prilocaine 2.5% cream) Topical Adhesive System

Sponsor:  
AstraZeneca LP

CSO:  
Laura Governale

Material Reviewed


Background and Summary Description:

In accordance with 21 CFR 201.57(f)(10), the sponsor submitted a geriatric labeling supplement on August 27, 1999.

Status Report

Reviews Completed:  CSO label review – April 20, 2000

CSO Review

Please note that the sponsor’s proposed revisions are indicated by strikeovers and underlined text. The agency’s proposed revisions will be bolded.

BOX WARNING:  N/A

DESCRIPTION:  No changes noted.

CLINICAL PHARMACOLOGY:  The following statement made by the sponsor should be placed in this section.

During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (~2.5 hours) than in younger patients (~1.5 hours).
No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients.

**INDICATIONS AND USAGE:** No changes noted.

**CONTRAINDICATIONS:** No changes noted.

**WARNINGS:** No changes noted.

**PRECAUTIONS:** The sponsor proposes to add the following geriatric claim in the last portion of the PRECAUTIONS section.

The Agency prefers to revise the Geriatric Use labeling as follows:

Of the total number of patients in clinical studies of EMLA, 180 were 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of EMLA are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of EMLA. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)
After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (~2.5 hours) than in younger patients (~1.5 hours). (See CLINICAL PHARMACOLOGY).

The following statement should be placed in the CLINICAL PHARMACOLOGY section as noted previously.

During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (~2.5 hours) than in younger patients (~1.5 hours). No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients.

ADVERSE REACTIONS: No changes noted.

DRUG ABUSE AND DEPENDENCE: N/A

OVERDOSAGE: No changes noted.

DOSAGE AND ADMINISTRATION: No changes noted.

HOW SUPPLIED: No changes noted.

This label may be approved with the above revisions.

________________________________________
Consumer Safety Officer

________________________________________
Medical Reviewer Comment/Concurrence

________________________________________
Supervisory Comment/Concurrence