

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 20-612**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

NDA 20-612

SUBMISSION DATE: 5/31/96

PRODUCT: Lidocaine Patch, 5%

BRAND NAME: Lidoderm™ Patch

REVIEWER: Dan Wang, Ph.D.

SPONSOR: Hind Health Care, Inc.

165 Gibraltar Court

Sunnyvale, CA 94089

TYPE OF SUBMISSION: Original

final

**SYNOPSIS**

This NDA was submitted for Lidocaine Patch, 5% for symptomatic treatment of pain in post-herpetic neuralgia. Each Lidocaine Patch contains 700 mg lidocaine (see detailed drug product description in appendix 1). One pharmacokinetic study was included in the submission to illustrate the systemic exposure of lidocaine after topical application of Lidocaine Patches at the maximum recommended dose (3 patches for 12 consecutive hours) for safety concern. The results show that 1) the systemic exposure of lidocaine is minimal. In healthy volunteers, the absorption of lidocaine was about 3% of the dose applied. The mean peak plasma concentration was about 128 ng/ml, which was well below those (6 µg/ml) known to induce systemic toxicity. 2) After 3 days of repeated dosing at this dose level, there was no evidence of accumulation in systemic concentrations. 3) It was also demonstrated that application of Lidocaine Patch to Post-Herpetic Neuralgia Patients and to Acute Herpes Zoster patients with un-healed herpetic lesions, did not result in increased lidocaine absorption. There does appear to be an age-related difference in systemic absorption, with older subjects absorbing less drug.

The applicant also included an in vitro/in vivo study in the submission. This study intended to examine the lot-to-lot variability with regard to permeation of lidocaine upon application of Lidocaine Patch to excised rat skin (in vitro) and human skin (in vivo). Due to large within/between subject variability and within/between lot variability, both in vitro and in vivo models failed to differentiate between different lots of manufactured product on the basis of drug release of Lidocaine Patch with the sample size studied.

Detailed reviews of above two studies can be found in appendix 2.

**RECOMMENDATION**

The applicant's Human Pharmacokinetics and Biopharmaceutics Section of NDA 20-612 is acceptable for meeting the requirements of 21 CFR 320, provided comments #1 to #5 on page 2 are adequately addressed.

**COMMENTS (need to be sent to the applicant):**

1. The assay validation data for pharmacokinetic study were not included in this NDA. The sponsor should submit full assay validation report to the Agency.
2. In the section of "Overall Summary - Pharmacokinetics", the applicant mentioned that pharmacokinetic data were also collected in Phase II and III studies. However, study reports of these two studies were not submitted in this NDA. The applicant should submit the reports once they become available and provide a timeline for the data.
3. Due to large within/between subject variability and within/between lot variability, both in vitro and in vivo models the applicant employed failed to differentiate between different lots of manufactured product on the basis of drug release of Lidocaine Patch with the sample size studied. The applicant is requested to develop an in vitro release method that would be able to investigate the drug release rate through a membrane. Such method should also be able to serve as a specification for quality control.
4. In pharmacokinetics section of the proposed labeling, some pharmacokinetic parameters listed does not agree with those obtained from the pharmacokinetic study submitted in this NDA. These parameters are: systemic clearance (0.33 - 1.15 L/min (mean  $0.78 \pm 0.22$ )); volume of distribution (0.7 - 2.7 L/kg (mean  $1.48 \pm 0.57$ )); half-life (82 - 257 minutes (mean  $114 \pm 44$ )). The applicant should give explanations for these numbers.
5. In pharmacokinetics section of the proposed labeling, it is indicated that  
However, in the  
pharmacokinetic study submitted, urine samples were not analyzed because of  
difficulties encountered in the assay technique. The applicant should provide  
scientific evidence for above sentence in proposed labeling.

**COMMENT (need to be conveyed to the Medical Officer):**

1. In the pharmacokinetic section of the labeling, it is indicated that  
This  
sentence should also be included in PRECAUTIONS section of the labeling.

IS  
Dan Wang

11/29/96  
Division of Pharmaceutical Evaluation III

FT initialed by D. Bashaw, Pharm.D. 4'OR 12/2/96

cc:

NDA 20-612(Original)

HFD-550(Clinical, Koerner)

HFD-880(N. Fleischer, Bashaw, Wang)

HFD-870(Clarence Bott, Drug, Chron Files)

HFD-205(FOI)

HFD-344(Viswanathan)

APPENDIX 1

## DRUG PRODUCT

### Components and Composition

The patches consist of a "sandwich" of an adhesive mixture containing the lidocaine, a non-woven polyester felt backing and a polyethylene terephthalate film release liner.

#### Adhesive Formula KN 48 (total amounts of each component)

Ingredient	mg/g adhesive	mg/patch	Kg/batch	Purpose
Lidocaine ✓				active
				diluent
Glycerin ✓				humectant
Sorbitol, 70% ✓				humectant
Polyacrylic acid ✓ 20% w/w				hydrogel matrix component
Sodium polyacrylate ✓				viscosity enhancer
Sodium carboxymethyl cellulose ✓				viscosity enhancer
Propylene glycol ✓				solvent
Urea ✓				humectant
Kaolin ✓				diluent
Tartaric acid ✓				pH adjustment
Gelatin ✓				viscosity enhancer
Polyvinyl alcohol ✓				viscosity enhancer
Dihydroxyaluminum/ aminoacetate ✓				cross-linking agent
Disodium edetate ✓				stabilizer
Methylparaben ✓				preservative
Propylparaben ✓				preservative
Total				

APPENDIX 2

## REVIEW OF INDIVIDUAL STUDIES

TITLE: Comparative Pharmacokinetic Study of Lidocaine Patches in Healthy Volunteers, Patients with Post-Herpetic Neuralgia, and Patients with Active Herpes Zoster

VOLUME: 2.5

INVESTIGATORS:

OBJECTIVES:

1. In healthy volunteers to describe blood levels of lidocaine that occur after topical, dermal application of Lidocaine Patch at maximum dose for 3 consecutive days, and to estimate the systemic dose of lidocaine absorbed.
2. To compare absorption from normal skin to that from skin compromised by the condition of post-herpetic neuralgia and compromised by incomplete healing of herpetic lesions.

FORMULATION: Lidocaine patch, 10 cm x 14 cm, 700 mg Lidocaine (5%).

STUDY DESIGN: This was a comparative pharmacokinetic study in which three groups of subjects were compared on the basis of their lidocaine blood level profiles, during and after topical application of Lidocaine Patches.

This study consists of three parts:

Study A: Normal Volunteers

Sixteen (16) healthy volunteers were recruited, 8 in the age range from 18-65 and 8 aged 65 years or older. Each group of 8 consisted of 4 males and 4 females. Each subject participated in 3 separate clinical sessions:

Session 1:

- 1) Lidocaine IV bolus. Volunteers received an IV bolus of lidocaine hydrochloride in the amount of 0.5 mg/kg body weight. This dose of lidocaine was chosen to produce peak blood levels above the expected peak levels from dermal application, but below systemic therapeutic levels for cardiac arrhythmia. Blood samples were withdrawn at  $t = 0, 1, 2, 5, 10, 15, 30, 60, 120, 180,$  and 240 minutes. The IV dosing study was used to provide data on clearance, volume of distribution and half-life. Clearance data was used to estimate systemic absorption of lidocaine after dermal dosing.

- 2) Single application of 3 Lidocaine Patches, 12 hours, 420 cm<sup>2</sup>. This session involved the simultaneous application of 3 patches, each 10 cm x 14 cm, for a total application time of 12 hours. The application was on a defined area on the back of volunteers. The three patches contain a total of 2100 mg of lidocaine applied over a 12 hours period. Blood samples were collected at t = 0, 1.5, 3, 6, 9, 12, 15, 18 and 24 hours. Urine was pooled for 24 hours.
- 3) Multiple application of 3 Lidocaine Patches, 3 x 12 hours, 420 cm<sup>2</sup>. This session involved 3, 12-hour application periods, with 3 patches applied during each period to a defined, 420 cm<sup>2</sup> area on the back of volunteers. The 12-hour application periods were separated by 12-hour "rest periods". The second and third applications each used 3 new patches, applied to the same defined area as the first application. The total lidocaine exposure for the 72 hour session was 6300 mg. Blood samples were collected at t = 0, 1.5, 3, 6, 9, 12, 15, 18, 24, 25.5, 27, 30, 33, 36, 39, 42, 45, 48, 49.5, 51, 54, 57, 60, 63, 66, 69, and 72 hours. Urine was collected and pooled for 0-24, 24-48 and 48-72 hours.

#### Study B: Acute Herpes Zoster (HZ) Patients

Twenty-two acute herpes zoster patients were recruited, 16 of whom had involvement on the torso. These patients were recruited soon after diagnosis, such that they were able to undergo the dermal application of Lidocaine Patches before complete healing of the lesions. Only patients with torso involvement had Lidocaine Patches applied under this protocol. This session involved the simultaneous application of 3 patches, each 10 cm x 14 cm, for a total application time of 12 hours. The application was on a defined area on the back of volunteers. The three patches contain a total of 2100 mg of lidocaine applied over a 12 hours period. Blood samples were collected at t = 0, 1.5, 3, 6, 9, 12, 15, 18 and 24 hours. Urine was collected over 24 hours.

#### Study C: Post-Herpetic Neuralgia (PHN) Patients

Thirteen post-herpetic neuralgia patients were recruited, 8 of whom had involvement on the torso. The study design was identical to Study B.

Additionally, in studies B and C with HZ and PHN patients, the Visual Analog Scale for pain (VAS) and the Category Relief measures were collected at some time points.

The studies were performed in two different study centers:

The studies in healthy volunteers were conducted in

The studies in HZ and PHN patients were conducted in

## ASSAY:

DATA ANALYSIS: Blood concentration time course of lidocaine and the major metabolite, monoethylglycinexylidide (MEGX) were determined during each of the clinical sessions, but the MEGX data were not included in this report. From the IV bolus, clearance (CL), volume of distribution and half-life were determined using non-compartmental techniques. C<sub>max</sub>, t<sub>max</sub> and AUC were determined for dermal application. The absolute dose of lidocaine absorbed from dermal application was estimated in the healthy group by multiplying the CL of lidocaine determined from the IV dose times the AUC of lidocaine measured during and after dermal dosing.

The 24 hour AUC data were analyzed by ANOVA, with age as a covariant in the model.

## RESULTS:

In healthy volunteer group, the evaluable number of subject is 15 with mean age of  $49.8 \pm 19.17$  years. The HZ group had 9 evaluable patients with mean age of  $53.67 \pm 19.07$  years, and the PHN group had 8 evaluable patients with mean age of  $69.62 \pm 11.25$  years.

Individual blood concentration data are shown in listing 2, 3, 4 for healthy volunteers and in listing 5 and 6 for patients. Estimated PK parameter values and some demographic information are presented in Tables 4.1 to 4.3 for healthy volunteers and in Table 5 for patients. The dose of lidocaine is in terms of free-base equivalent, since Lidocaine Patch contains the free-base of lidocaine and the IV control was lidocaine hydrochloride.

The results show that after IV dosing in healthy volunteers, the mean clearance of lidocaine is  $0.635 \pm 0.175$  L/min and terminal half-life is  $106.9 \pm 22.0$  minutes. The mean dose absorbed were about  $63.8 \pm 32.5$  mg ( $3 \pm 1.6\%$ ) after 12 hours Patch loading and  $188.2 \pm 72.2$  mg ( $3 \pm 1.2\%$ ) after 3 x 12 hours Patch loading. The highest peak concentration after dermal application observed was 277 ng/ml, with the lowest at 37 ng/ml.

Figure 1 shows the mean blood level profiles from Lidocaine Patch application for each of the three subject groups, with the healthy volunteers having two curves for each of the two topical application sessions. The three-day profile in normal volunteers shows no evidence of systemic build-up over time, either in the C<sub>max</sub> or in the trough levels at the end of each consecutive 24 hour period. The mean C<sub>max</sub> is the highest in normal

volunteers ( $127.8 \pm 63.3$  ng/ml), the second in HZ patients ( $82.5 \pm 43.3$  ng/ml) and the third in PHN patients ( $52.1 \pm 30.6$  ng/ml). The mean AUC values for each group also have the same descending order. The  $t_{max}$  values for each group are similar.

The sponsor also did a regression analysis for AUC versus age (Figure 2). There is a general trend for the AUC to decrease with increasing age. The  $C_{max}$  values were plotted versus age in Figure 3 and also showed a similar trend. The 24 hour AUC data for 3 groups (healthy, HZ and PHN) were analyzed by ANOVA, with age as a covariant in the model. The results showed that there appears to be a statistically significant difference with respect to age ( $p=0.0472$ ). However, the difference with regard to group is not statistically significant ( $p=0.0953$ ).

#### CONCLUSIONS:

1. After topical application of Lidocaine Patch, the systemic exposure of lidocaine is minimal. In healthy volunteers, the absorption of lidocaine after 12 hours topical application of 3 Lidocaine Patch which contain 2,100 mg lidocaine was about 3%.
2. At the maximum recommended dosage in healthy volunteers, there is no evidence of a build-up in systemic concentrations after 3 day repeated dosing.
3. Application of Lidocaine Patch to HZ patients with un-healed herpetic lesions, does not result in increased lidocaine absorption. There does appear to be an age-related difference in systemic absorption, with older subjects absorbing less drug.

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