

MEDICAL TEAM LEADER REVIEW

APR 10 1997

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION -- HFD-550

NDA #: #20-612
SUBMISSION DATE: June 11, 1996.
REVIEW DATE: March 22, 1997.
REVIEWER: John Hyde, Ph.D., M.D.
Medical Team Leader.

NAME: Lidoderm (lidocaine 5%) Patch.
SPONSOR: Hind Pharmaceutical
165 Gibraltar Court
Sunnyvale, CA 94089

PHARMACOLOGIC CATEGORY: Anesthetic
PROPOSED INDICATIONS: Post-herpetic neuralgia
DOSAGE FORM & ROUTE: Topical patch
NDA DRUG CLASSIFICATION: 3S
RELATED REVIEWS: Medical Officer Review 10/11/96
Statistical Review 10/3/96
C. Koerner

CSO:

Abstract

The primary medical reviewer favors approvability of this NDA. However, the Medical Team Leader does not find that the application provided substantial evidence of efficacy, and it is recommended that the application be deemed non-approvable. The IND record is also reviewed concerning the understandings about the number of pivotal studies that would be required for this NDA.

RESUME:**Efficacy Evaluation**

The sole phase 3 study in the NDA is the two-center study of Lidoderm Patch vs. placebo patch in post-herpetic neuralgia (PHN). The study also involved the gel, but that portion of the study is not part of the study report in this NDA. The primary analysis is described in the protocol as follows (NDA vol. 2.8, p. 1515):

"The proposed primary statistical variables will be:

- the change from pretreatment VAS pain rating over time during the first two test sessions,
- the change from pretreatment Total Side Effect Checklist over time during the first two test sessions, and

- Relief scores over time during the first two test sessions.

In the applicant's Table 4 on p. 1436 in vol. 2.8, none of the p-values are close to statistical significance for VAS reduction in session one ($p > .4$ at each observation, and $p=.695$ for the average). At session two a significant difference in VAS reduction was seen only at 2 hours, and $p=.109$ for the average reduction.

In Table 6 on p. 1438 of vol. 2.8, relief scores in session one are statistically significant only at 10 hours; p-values for all other times are $>.24$, and $p=.334$ for the average. In session two, relief scores have $p>.15$ at all observation times, and $p=.116$ for the average relief score.

The side effects checklist is a safety, rather than efficacy, endpoint. It showed no statistically significant differences in sessions one or two (Table 10, vol. 2.8, p. 1463).

Regarding secondary endpoints the protocol states (vol. 2.8, p 1516):

"The proposed secondary statistical variables will be:

- the QST scores over time for all three test sessions,
- VAS pain, Relief, and Total Side Effect Checklist rating for the third test session,
- weekly composite categorical pain relief rating, and
- global rating of average daily pain intensity ratings."

"QST" is the abbreviation for quantitative sensory testing. It refers to thermal sensory testing, but not allodynia testing. This reviewer did not find an analysis of QST scores in the report or appendices. The study report description of the testing states that QST was optional, although it was not described that way in the protocol.

The results for the third session (at the end of one month) found no statistically significant differences for VAS or side effects checklist, but there was a statistically significant difference ($p=.021$) for the pain relief score (Table 8, vol. 2.8, p. 1440).

This reviewer did not find an analysis of the weekly composite pain relief ratings.

The daily pain intensity results were presented in Table 7 (vol. 2.8, p. 1439), and showed no statistically significant differences.

The sponsor included an analysis of dynamic allodynia testing. This endpoint was not clearly described in the protocol, but it is described in the study report (vol. 2.8, p. 1417): after 6 hours, the maximally painful area

was stroked for 5 cm in 1 second with a 1" foam brush; this was repeated two more times allowing 1 second between each of the three strokes. Pain was recorded on a 4-point scale (0=no pain, 3=extreme pain). Table 5, on p. 1437 of vol. 2.8, showed statistically significant differences at sessions 1 and 2 ($p < .001$ and $p = .018$, respectively).

The study report also included analyses of each study site. When the sites are considered separately, neither stands alone. The only significant finding reported for the UW site was session 3 pain relief, and the only significant finding reported for the UCSF site was allodynia reduction at session 1.

Number of Studies Required

There has been some confusion about whether the applicant was expected to provide one or two positive phase 3 studies. Therefore, the IND jackets and division files were reviewed. The sponsor has a closely related IND for lidocaine gel 5%, and several submissions and meetings pertained to both products.

On 10/9/90, IND [redacted] for lidocaine gel 5% was submitted, and on 6/14/91 IND [redacted] for this product (lidocaine patch 5%) was submitted. Both included phase 2 study protocols.

On 7/24/92, an end-of-phase 2 meeting was held for the gel and attended by the division director (at that time the division was not under an Office). A package submitted 6/30/92 (gel IND vol. 3.1) tried to make the case that no phase 3 study was needed. However, FDA minutes indicate that the division felt Lidoderm's effectiveness still needed to be clearly established. Studies comparing to EMLA cream were suggested.

On 10/2/92, the sponsor submitted a general correspondence to the gel IND (vol. 3.1) outlining the development plan, which included only one study in post-herpetic neuralgia (PHN). At an internal division meeting on 11/30/94 (vol. 3.1 of gel IND) it was stated that "In general, the principles fundamental to the planned studies are acceptable." The sponsor apparently received a copy of the minutes, as they made reference to them in a 12/16/92 submission (patch IND vol. 1.1). However the division director wanted the sponsor to study use in venepuncture because off label use for that purpose was anticipated. A telecon was held on 2/5/93, and in a submission dated 2/16/93 (gel IND vol. 3.1), the sponsor consented to a venepuncture study, although they did not intend to seek that as a indication. It is not clear whether the division expected that such a study would be used as evidence for the product's effectiveness in addition to the PHN study.

On 5/24/94, a meeting was held with the sponsor to discuss the development of the gel and patch. The phase 3 PHN study, using both patch and gel was

already underway. The meeting was attended by the acting division director. In the sponsor's submission of 5/27/94, following the meeting (patch IND vol. 5.1), it was noted that the issue of one pivotal study was discussed and that there was "no objection to the plan as outlined." However, a submission of 8/18/94 (patch IND vol. 5.1) refers to the question raised during the 5/24/94 meeting concerning the number of studies. Apparently the question had been discussed by phone (according to sponsor's letter, no telecon notes are available). The sponsor proposed in the 8/18 letter that the two-center, phase 3, PHN study would be enlarged slightly, so that "Data from each center will therefore stand on its own as a pivotal study for patch efficacy." (The next year's annual report, of 8/15/95, mentioned the increase in sample size for that study.)

The sponsor's annual report of 8/15/95 (IND vol. 6.1) makes reference on last page to a meeting held in 12/94, although there are no minutes in the record that meeting. The annual report states that the division proposed that, if the sponsor studied both PHN and painful diabetic neuropathy, then both indications could be approved.

The sponsor requested an informal meeting, which was held 5/25/95 (minutes in division file). Development was reviewed and problems with the study of diabetic neuropathy were discussed. The acting division director was not present. The issue of two pivotal studies was discussed again. The division's minutes state that "The offer by PDES to the sponsor for two indications with two good, well-controlled double blinded, clinical trials for PHN and diabetic neuropathy, was made again." The sponsor's 6/27/95 summary of that meeting acknowledged the division's concern about having only one pivotal study, but the sponsor seemed to feel they would have enough to file for PHN.

DISCUSSION & CONCLUSIONS:

The phase 3 study does not provide substantial evidence for efficacy by the usual standards. Analysis of the primary endpoints does not establish a difference from placebo patch, and results for secondary variables are sparse. Both the applicant and the primary reviewer noted the substantial difference in allodynia reduction, and viewed that finding as the evidence for efficacy.

Although the allodynia results appear rather impressive, this reviewer cannot accept those results in this one study (and mainly driven by the UCSF site result) as substantial evidence of efficacy. Comparison of allodynia did not appear in the protocol as either a primary or secondary endpoint. Allodynia reduction apparently was not considered to be an indication by the sponsor until the results of this study were available. There is also reason to question the clinical relevance of allodynia as measured in this study. The response was evoked in a controlled setting; it is not clear how pertinent that was to the allodynia of daily living or what contribution allodynia made to the discomfort of PHN in this study. While it

is reasonable that it could be important, the allodynia reduction effect was not strong enough for it to have a substantial impact on the daily global pain intensity ratings.

It is not completely clear from the record exactly what the division's expectations were for developing this NDA, and it is quite possible there was not a clear understanding between sponsor and division about what those expectations were. There was no properly constituted end-of-phase 2 meeting for the Lidoderm Patch. The end-of-phase 2 meeting for the gel did not conclude with a final agreement, because the sponsor did not have any explicit phase 3 study proposals at the time of the meeting. It did seem, however, that the sponsor understood the division's desire for some sort of evidence of reproducibility, because the issue of one pivotal study came up for discussion repeatedly, and the sponsor proposed having each the two centers in the PHN study stand alone.

RECOMMENDATIONS:

The application should not be approved for the reason covered by 21 CFR 314.125 (b)(5): lack of substantial evidence that the product has the purported effect.

If the applicant chooses do additional studies to respond the non-approvable action, the division should make sure that any agreements, that set out the requirements for substantial evidence of efficacy, are clearly identified and well documented. The specific intended indication should be made explicit. The requirements should include some sort of demonstration of the reproducibility of the results.

Orig NDA # 20-612
HFD-550/Div File
HFD-340
HFD-550/CSO/Koerner
HFD-550/Chem/Yaciw
HFD-550/Pharm/Yang
HFD-550/Stat/Stein
HFD-550/Biopharm/Bashaw
HFD-550/MO/JHyde

/S/
John E. Hyde, Ph.D., M.D.

Concur.

[Signature] 4/12/97
Acting Div Director

MEDICAL OFFICER REVIEW

NDA Number: 20-612
Drug Name: Lidocaine 5% dermal delivery system (patch)
Trade Name: Lidoderm™
Sponsor: Hind Health Care, Inc.
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Date Submitted: June 1, 1998
Date Received for Review: July 30, 1998
Medical Reviewer: Christina Fang, M.D.
Secondary Reviewer: John Hyde, M.D., Ph.D.
Drug Class: Local anesthetics
CSO Contact: Victoria Lutwak

/S/

12/1/98

JEN

12-1-98

Christina Fang, M.D. Date

Team Leader Date

CC: Original NDA 20-612
HFD-550/Division File
HFD-550/C. Fang/V. Lutwak/C. Yaciw/W. Yang/D. Wang
HFD-340
R/D Init. by:
F/T by:

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I. Background information

1. Introduction

Postherpetic neuralgia (PHN) is characterized by persistent pain and increased skin sensitivities (dysesthesia, allodynia) after skin lesions of herpes zoster (HZ) are healed. It occurs in about 20% of all HZ patients. The incidence increases with age: 10% in patients age ≥ 40 and 20-50% in patients age ≥ 60 (Raj, 1993). Older patients are more likely to have more debilitating disease, longer duration of pain, and suffer more complications. The two main types of discomfort are persistent intractable pain (may have some relief during sleep) and dysesthesia, which is often aggravated by light touch and improved with heavy steady pressure. The condition may improve slowly: about 50% of all PHN cases resolve in 5 months and only slightly more than 20% cases have persistent pain for more than one year (Hetherington, 1998). Of those who have persistent pain for more than one year, 50% improve over time and 25% become more intractable (Watson, 1991).

Lidocaine is an amide-type local anesthetic agent that has been shown to have analgesic activities when applied topically at various concentrations. Up to 4% lidocaine in a topical vehicle have been considered as generally safe and effective anesthetics for OTC use based on the tentative monograph for external analgesics.

The sponsor has developed a lidocaine 5% dermal delivery system (DDS), also called lidocaine patch. Each patch (10cm x 14cm) contains 700mg lidocaine in adhesive materials applied to non-woven polyester backing. The patches are to be applied to intact skin over a limited skin surface area of 420cm^2 (70in^2) for post-herpetic neuropathic pain indication.

2. Previous clinical studies

(1) Pharmacokinetic studies

Pharmacokinetic (PK) profile of the patch includes 3% absorption and a mean peak plasma concentration of 128ng/ml after applying 3 patches simultaneously for 12 hours in healthy volunteers, no evidence of accumulation after repeated dosing (3 patches for 12 hour) for three days in the volunteers, and no evidence of increased absorption when the patches were applied to the skin of post-herpetic patients or to the unhealed herpetic lesions.

(2) Clinical trials

Two clinical trials were conducted in patients with chronic post herpetic neuropathic pain and were submitted in the original NDA in June 1996. The key features and the results of these trials will be briefly described here.

The first trial was a single-center, single-dose (12 hour application), vehicle- and no treatment-controlled, four-way crossover (two lidocaine arms, one vehicle arm, and one no treatment arm) study. A total of 40 patients was enrolled and 35 were evaluable for efficacy. The sample population was characterized by baseline pain of at least moderate in intensity (corresponding to a score of ≥ 25 mm on a 100mm VAS scale), and substantially greater the pain induced by innocuous mechanical stimuli to the maximally painful area than the background pain. Patients were allowed to be on stable oral analgesics throughout the trial. Pain intensity (PI) and pain relief (PR) were evaluated periodically at 0.5, 1, 2, 4, 6, 9, and 12 hours.

Statistically significant differences in favor of lidocaine patch to vehicle patch were shown in PI scores from 4 to 12 hours, and that in favor of vehicle patch to no treatment arm were shown in PI scores at 2 and 6 hours and in PR scores at 30 minutes and from 2 to 6 hours. Analgesic onset and duration were not evaluated. Allodynia was measured by gently brushing a cotton swab across the skin for 3 times using a 4-point categorical scale at hour 6 of patch application. The reduction in allodynia was 41% in lidocaine arm, 32% in vehicle arm, and 12% in no treatment arm as reported by the sponsor, though allodynia was not defined as an efficacy parameter and data were not analyzed statistically. In summary the findings did not support acute analgesic efficacy.

The second trial was a two-center, vehicle-controlled, parallel study conducted in 171 patients (150 evaluable for efficacy: 100 on lidocaine and 50 on vehicle patches), who were enrolled based on the same selection criteria as described above. The study had 3 phases. The single-dose effect was evaluated in the first 2 phases, in which patches were started at least 48 hours apart, using PI and PR as primary efficacy parameters. No efficacy was demonstrated in either phase. The findings of substantially different allodynia reduction at hour 6 in single-dose study phases were exploratory in nature. The results were confounded by post-hoc nature of analysis (not defined as efficacy parameter in the original protocol or any protocol amendment) and questionable clinical relevance with on the type of measurement.

The multiple-dose effect was evaluated in the third phase of the study. Patients were allowed to use up to 3 patches simultaneously for up to 12 hours in a 24-hour period for 21 to 28 days, starting a week after the second phase. A significant difference was shown in PR, which was evaluated only once at the final visit (and thus subject to recall bias in this reviewer's opinion). No significant differences were shown in weekly comparison of daily average PI or in PI at the final visit. In addition, patients on vehicle patch after repeated dosing experienced a substantial reduction in PI (33%, $p=0.0001$) from baseline and the reduction was of the similar magnitude as that of the active treatment (40%, $p=0.0001$). In addition, allodynia was evaluated at the final visit, but the result was not reported. To summarize, efficacy was not demonstrated in terms of either single-dose effect or multiple-dose effect.

(3) Dermatological safety studies

The sponsor also conducted standard primary irritation, contact sensitization, and photo contact sensitization studies and had negative findings.

3. Interaction between the sponsor and the agency

Based on the records of the subsequent communications between the sponsor and the division, an agreement was to use a withdrawal study design to assess patient's response to the discontinuation of treatments when lidocaine patch and vehicle patch were compared in a crossover fashion.

II. Current study

1. Protocol (No. CX2A2005)

(1) Study design

This was a multiple-dose, randomized, double-blind, vehicle-controlled, 2-way crossover study of lidocaine 5% dermal delivery system (DDS) conducted at 2 centers in the United States.

(2) Eligibility

Eligible subjects were patients with the diagnosis of post-herpetic neuralgia who were regular users of lidocaine patch, and were identified as responders (able to obtain moderate pain relief) in the open-label studies (open-label extension of previous controlled clinical study, and open-label compassionate-use study). Patients were also required to use the patch only if they had increased pain.

(3) Treatments

Subjects were randomly assigned to receive one of the treatments, lidocaine patch or vehicle-control patch, for a maximum of 14 days, followed by the other treatment in a crossover fashion with no washout period in between. Subjects were instructed to apply the patch following the same usage pattern as what they practiced during the open-label phase. Oral analgesics were allowed at prescribed levels, but topically applied medication over the skin of painful area was not permitted.

(4) Assessments

Daily telephone interviews were conducted to obtain information about dosing, efficacy, and safety, specifically: the time of patch application and removal, daily pain relief on a 6-point categorical scale (worse, no relief, or slight, moderate, a lot, or complete relief), concomitant analgesics, and adverse events.

(5) Efficacy parameters

Subjects were to exit a treatment phase if their pain relief were 2 points lower than their usual response to lidocaine patch experienced during open-label use for 2 consecutive days. The primary efficacy variable was defined as the time to exit from the treatment phase and the secondary efficacy variable as subject's preference of treatment phase based on perceived benefit.

2. Results

(1) Patient profile (Attachment 1)

The sample population was consisted of male and female subjects (8 males, 13 females, and gender not reported for the rest of the group) age ranging from 65 to 97 (mean age at 77).

Prior to the start of the first treatment phase, there was no statistically significant difference between the lidocaine and the vehicle-control arm in terms of the length of previous use of patches. Patient's experience with lidocaine patch was 3.3 years on the average, ranging from 2.7 months to 8.5 years.

Out of the 32 subjects who received treatment, 30 completed the study. Two patients discontinued earlier from the vehicle-control arm in the second treatment phase: day 4 and day 6, respectively. It was due to increased pain and insomnia in one case and rash in the second case.

(2) Efficacy

(i) Time to exit (Attachment 2.1-2.3)

None of the patients on lidocaine patch exited the treatment phase earlier than 14 days. The differences between the two treatments in terms of time to exit were statistically significant. And there were no discrepancies between the treatment phases as shown in the table below.

Treatment phase	Patch	Time to study exit		p-value
		Median: days	95% conf. int.	
First	Lidocaine	>14	14.0, >14	<0.001
	Vehicle	2.7	2.0, 4.0	
Second	Lidocaine	>14	14.0, >14	<0.001
	Vehicle	6	4.0, >14	
Total	Lidocaine	>14	14.0, >14	<0.001
	Vehicle	3.8	3.0, >14	

The sequence analysis for study exit time did not indicate carry-over effects.

(ii) Pain relief (Attachment 3.1-3.6)

The mean daily relief scores for patients on lidocaine patch were 1.2 to 1.6 points (based on 6-point scale) higher (better relief) than those on vehicle patch. The 95% confidence intervals about the means for the treatment groups basically did not overlap. Again, no discrepancies were noticed between the treatment phases.

(iii) Patient's preference of treatment

Twenty-five (78%) patients preferred lidocaine treatment; 3 (9%) preferred vehicle treatment; 4 (12%) had no preference. The difference between the active and vehicle treatments was statistically significant at $p < 0.001$.

(iv) Concomitant medication (Attachment 4)

About 50% patients took oral medications, such as antidepressant, narcotic and non-narcotic analgesics, which have been commonly used in the symptomatic treatment of PHN. There were no statistically significant differences between the treatment groups in terms of the ratio of the number of days on concomitant medication (oral medication for neuropathic pain) to the number of days on patches.

(3) Safety

(i) Drug exposure

Most patients (24 of 32) used ≤ 3 lidocaine patches (simultaneously applied) up to 12 hours in a 24-hour period for 14 days in the current study. Two patients used 4 patches and one used 5 patches. Six patients had patches on for more than 12 hours and the longest single application was 22.5 hours.

(ii) Adverse events

Adverse events were reported by one third of the patients in each group and mostly were minor complains mild in severity. The remarkable findings associated with the patches were local application site reactions, which were reported by 9 (28%) patients on lidocaine and 11 (34%) on vehicle patches.