

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-612

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-612

NOV 21 1996

REVIEW #1

DATE REVIEW COMPLETED: 11/20/96

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	5-31-96	6-12-96	6-26-96
AMENDMENT	9-25-96	9-26-96	10-03-96
AMENDMENT	10-09-96	10-16-96	10-24-96

NAME & ADDRESS OF APPLICANT: Hind Health Care, Inc.
165 Gibraltar Court
Sunnyvale, CA 94089

DRUG PRODUCT NAME

Proprietary: Lidoderm™ Patch
Established: Lidocaine USP
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY:

Topical analgesic (painful skin due to shingles)

DOSAGE FORM:

Dermal patch

STRENGTHS:

5% w/w (700 mg/patch)

ROUTE OF ADMINISTRATION:

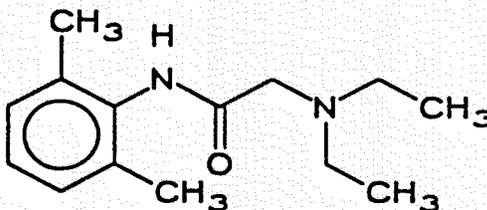
topical

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide
CAS 137-58-6; Mol. Form. C₁₄H₂₂N₂O; Mol. Wt. 234.34



REMARKS:

1. This product has been granted orphan status for the treatment of post-hepatic neuralgia (painful skin due to shingles).
2. Many of the specifications and methods (including those in the stability section) are based on amount per gram of adhesive. They should be revised to amount per patch.
3. The Proprietary name, Lidoderm Patch, has been submitted to the Labeling and Nomenclature Committee for comment. No response has been received as yet. A copy of the request is attached.

CONCLUSIONS & RECOMMENDATIONS:

1. EER was sent 7/22/96 and has not been completed as yet.
2. EA report was reviewed separately and found unacceptable. The deficiencies are included in the attached list on page 22.
3. Normally the CMC section of this NDA would be NOT approvable since there are numerous deficiencies (see attached list), however, since this is an orphan drug, these deficiencies may be conveyed in an approvable letter.

cc:

Orig. NDA 20-612
HFD-550/Division File
HFD-550/CYaciw
HFD-550/CKoerner
HFD-550/Neuner
HFD-880/Bashaw

IS/

Charlotte A. Yaciw,
Chemist, HFD-550/830

IS/

11-21-96

filename: N20612C1.REV

Hasmukh B. Patel
Chemistry Team Leader HFD-550

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-612

REVIEW #2

DATE REVIEW COMPLETED: 7/14/98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
[SUBMISSION	5-31-96	6-12-96	6-26-96
AMENDMENT	9-25-96	9-26-96	10-03-96
AMENDMENT	10-09-96	10-16-96	10-24-96]
AMENDMENT (BC)*	8-30-97	9-4-97	9-15-97
AMENDMENT (AZ)*	6-1-98	6-2-98	
AMENDMENT (BC)*	6-24-98	7-1-98	

*Submissions covered by this review

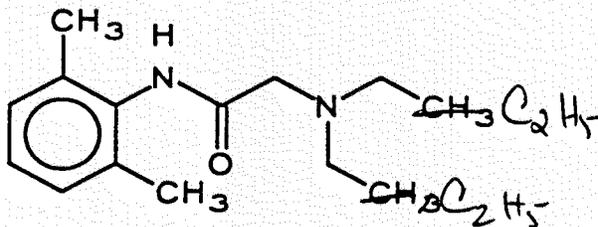
NAME & ADDRESS OF APPLICANT: Hind Health Care, Inc.
165 Gibraltar Court
Sunnyvale, CA 94089

DRUG PRODUCT NAME

Proprietary: Lidoderm™ Patch
Established: Lidocaine USP
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Topical analgesic (painful skin due to shingles)
DOSAGE FORM: Patch
STRENGTHS: 5% w/w (700 mg/patch)
ROUTE OF ADMINISTRATION: topical
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide Mol. Form. C₁₄H₂₂N₂O; Mol. Wt. 234.34
CAS 137-58-6;



REMARKS:

◆The L&NC has found the name Lidoderm acceptable, however, they recommend the use of "transdermal patch" for the dosage form. This is incorrect since this is NOT a transdermal product. The Nomenclature Standards Committee (CDER lexicography) has decided that this product should be called a "patch".

◆The 8/30/97 amendment contains the following information (note that the volume IDs in the amendment do not match FDA's). Each volume has separate (single) pagination.

FDA volume 4.1- Responses to the NA letter.

FDA volume 4.2 - Not CMC (protocol)

FDA volume 4.3 - A revised CMC section with no notation of what was revised.

FDA volume 4.4 - "Methods Validation." Actually the process validation report and copies of the analytical sections

FDA volume 4.5 - Environmental assessment. Firm representative has been requested to determine the status of this NDA under the 1997 rewrite. See 6/23/98 amendment.

FDA volume 4.6 - Laboratory validation package.

◆The 6/2/98 amendment references the CMC to the 8/30/97 submission. This is the amendment which restarted the review clock.

◆The 6/23/98 submission contains the claim for categorical exclusion from EA.

CONCLUSIONS & RECOMMENDATIONS:

1. This NDA is approvable provided the attached comments are adequately addressed.
2. Hind should be notified that Lidoderm Patch may be assigned a 36 month expiration period based on the submitted stability data.
3. The microbiology portions of the 8/30/97 amendment should be sent to Microbiology for consult review.

cc:

Orig. NDA 20-612
 HFD-550/Division File
 HFD-550/CYaciw
 HFD-550/VLutwak
 HFD-880/Bashaw
 HFD-830/chen

JSI

Charlotte A. Yaciw, Chemist, HFD-550/830

JSI

7-20-98

filename: N20612C2.REV

Hasmukh B. Patel, Chemistry Team Leader HFD-550

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-612

REVIEW #3

DATE REVIEW COMPLETED: 8/24/98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
[SUBMISSION	5-31-96	6-12-96	6-26-96
AMENDMENT	9-25-96	9-26-96	10-03-96
AMENDMENT	10-09-96	10-16-96	10-24-96
AMENDMENT (BC)	8-30-97	9-4-97	9-15-97
AMENDMENT (AZ)	6-1-98	6-2-98	
AMENDMENT (BC)	6-24-98	7-1-98]	
AMENDMENT (BC)*	8-04-98	8-05-98	8-18-98

*Submission covered by this review

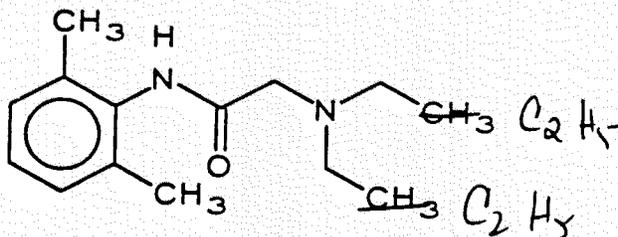
NAME & ADDRESS OF APPLICANT: Hind Health Care, Inc.
165 Gibraltar Court
Sunnyvale, CA 94089

DRUG PRODUCT NAME

Proprietary: Lidoderm™ Patch
Established: Lidocaine USP
Code Name/#:
Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY: Topical analgesic (painful skin due to shingles)
DOSAGE FORM: Patch
STRENGTHS: 5% w/w (700 mg/patch)
ROUTE OF ADMINISTRATION: topical
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide Mol. Form. C₁₄H₂₂N₂O; Mol. Wt. 234.34
CAS 137-58-6



REMARKS:

◆ The L&NC has found the name Lidoderm acceptable, however, they recommend the use of "transdermal patch" for the dosage form. This is incorrect since this is NOT a transdermal product. The Nomenclature Standards Committee (CDER lexicography) has decided that this product should be called a "patch".

◆ The 8/04/98 amendment contains the responses to the deficiencies noted in Review #2 which were conveyed by FAX on July 21, 1998.

◆ The microbiology portions of the 8/30/97 amendment were sent to Microbiology for consult review.

◆ The following items are still pending:

Agreement on whether the adhesive strength test should have an upper limit.

Microbiology consult

Methods validation at FDA labs

CONCLUSIONS & RECOMMENDATIONS:

1. This NDA is **approvable** until the adhesive specification issue is resolved.
2. Hind should be notified that Lidoderm Patch may be assigned a 36 month expiration period based on the submitted stability data.

cc:

Orig. NDA 20-612

HFD-550/Division File

HFD-550/CYaciw

HFD-550/VLutwak

HFD-880/DBashaw

HFD-830/CWChen

filename: N20612C3.REV

JSI

Charlotte A. Yaciw, Chemist, HFD-550/830

Revised 10/15/98

JSI

11-1-98

Hasmukh B. Patel, Chemistry Team Leader HFD-550

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-612

PHARMACOLOGY REVIEW(S)

final

**DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC
DRUG PRODUCTS
PHARMACOLOGY AND TOXICOLOGY REVIEW**

NDA 20-612

DRUG: Lidoderm Patch (Lidocaine 5% w/w)

SPONSOR: Hind Health Care, Inc.
165 Gibraltar Court
Sunnyvale, CA 94089

SUBMISSION DATE: May 31, 1996

TYPE OF SUBMISSION: Original Full Application

DATE COMPLETED: November 8, 1996

REVIEWER: W. C. Josie Yang, Ph.D.

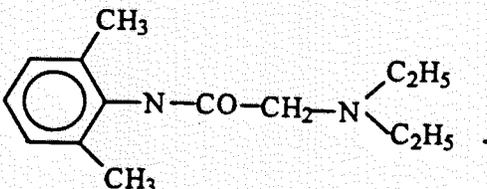
CDER STAMP DATE: June 11, 1996

DATE RECEIVED IN HFD-550: June 12, 1996

DATE ASSIGNED TO REVIEWER: June 27, 1996

DRUG CATEGORY: Topical Anesthetic

FORMULA: 2-(Diethylamino)-N-(2,6-dimethylphenyl)
Acetamide; C₁₄H₂₂N₂O; MW=234.33

CC1=CC=C(C=C1C)N(C(=O)CCN(C)C)C

INDICATION: Treatment of Pain in Post-Herpetic Neuralgia (Shingles)

DOSAGE FORM: Adhesive Patch (10x14 cm²)

RELATED DRUG/INDs/NDAs/DMFs: IND [] IND [] DMF [] NDA8-048;
NDA8-816; NDA9-470; [] []

PRECLINICAL/LABORATORY STUDIES:**PHARMACOLOGY**

No new studies were included in this submission.

TOXICOLOGY

Two studies were submitted in the current NDA to evaluate the potential of Lidoderm patch to induce dermal irritation in rabbits and skin sensitization in guinea pigs.

1. Evaluation of the Dermal Irritation of Lidocaine Formulations (Lidocaine Poultrice, Lidocaine Gel) in Rabbits.

Study N^o: B90008

Protocol N^o: P01893

Study Aims: To assess the dermal irritation of Lidocaine poultrice, Lidocaine gel in Rabbits.

Compound: 5% Lidocaine poultrices on patches containing 0.1g of adhesive per cm² (Lot N^o: KN48), 5% Lidocaine gel (Lot N^o: 3010, Formula 19), and 5% Xylocaine ointment (Astra Pharmaceutical Products, Lot N^o: 906122)

Control Vehicle: placebo poultrice (Lot N^o: KN49) and placebo gel (Lot N^o: 2280)

Dose & Route: topical skin application for 24 hr

Animal: 24 ♀ rabbits, weighing 1.88-2.42 kg, 6/group

Study Location:

Compliance with GLP/QAU: Yes

Study Date: 04/17/90 - 04/25/90

Study Design: Rabbits were randomly divided into 4 treatment groups as follows. The trunks of animals were shaved 24 hr before the application of the test articles. The right side of each rabbit from all groups but group D was abraded with 18G needle and the left side was left intact. The test articles and corresponding placebos were applied to each side of the rabbits. Blood was drawn at 1, 3, 8, 24, and 30 hr post application of the test article from rabbits in groups A-C and at 1, 3, 8, 24, 48, 72, 96, and 120 hr post application of the test article from the rabbits in the group D. Adhesive was removed after 24 hr post application of the test article. Serum Lidocaine concentrations were analyzed. Skin irritation scores were recorded at 1, 24, 48, and 72 hr after poultrice removal.

Group	N ^o Animal/Group	Treatment
A	6	6.25 cm ² 5% Lidocaine poultrice and placebo poultrice for 24 hr
B	6	6.25 cm ² (625 mg) 5% Lidocaine gel and placebo gel for 24 hr
C	6	6.25 cm ² (Xylocaine ointment) (625 mg) for 24 hr
D	6	7 x 10 cm ² whole poultrice for 5 days (Unabraded test site)

Results: No skin irritation was noted. Little (one in group B at 1 hr, one in group C at 8 hr and one in group C at 24 hr post application with values of 0.11- 0.16 µg/ml) or no serum

Lidocaine levels were detected in the blood samples taken from each group. The sensitivity of the Lidocaine detection assay was $\geq 0.1 \mu\text{g/ml}$. Therefore, various Lidocaine formulations (poultice, gel or ointment) did not elicit skin irritation in the present test.

2. Lidoderm Patch: Skin Sensitization Study in Guinea pigs (Modified Buehler Topical Closed Patch Technique).

Study N^o: LSC 3194-M009-92

Protocol N^o: P01893

Study Aims: To assess the dermal sensitization potential of Lidocaine patch in guinea pigs.

Compound: Lidocaine patch formula N^o KN48 (Lot N^o: 81081), 10 x 14 cm² patch containing 700 mg of Lidocaine; 20 mg Lidocaine and 2 x 2 cm²/application.

Positive Control: Dinitrochlorobenzene (DNCB) (Sigma Chemical Co., Lot N^o: 80H0121) in 80% (v/v) Ethanol.

For Induction: 4 ml of 0.4% (w/v) DNCB solution

For Challenge: 0.4 ml of 0.2% (w/v) DNCB solution

Dose & Route: topical skin application,

For Induction: 2 x 2 cm²/application, 6 hr/application, 1x/week for 3 weeks

For Challenge: 14 days post last application, 2 x 2 cm² patch was applied to the untreated site for 6 hr

Animal: 21 σ & 21 f adult Hartley albino guinea pigs, weighing 334-389 g for the σ and 315-389 g for the f , 5/sex/group for Lidocaine test and 3/sex/group for DNCB test.

Study Location:

Compliance with GLP/QAU: Yes

Study Date: 02/04/92 - 03/13/92

Study Design: Groups of 5/sex or 3/sex guinea pigs were treated with a 20 x 20 mm² pad of test article, a blank Webril^o pad, 0.4 ml DNCB or 0.4 ml 80% ethanol on the shaved left flank 1x weekly for 3 weeks. The induction exposure for Lidocaine patch and its control, sham treatment, was 6 hr. The application sites were scored for erythema 24 hr after removal of wraps. Animal assignment and grouping were shown in the following table. Two weeks after the last induction application, guinea pigs were challenged with Lidocaine patch or DNCB on the shaved right flank. The challenge sites were evaluated for skin irritation (erythema/edema) 24 hr post challenge treatment.

Group	Induction	Challenge	Rechallenge	N ^o of Animals
1. Lidocaine Test	Lidocaine Patch	Lidocaine Patch	Lidocaine Patch	5/sex
2. Negative Control	Sham Treatment	Lidocaine Patch	-	5/sex
3. Rechallenge Control	-	-	Lidocaine Patch	5/sex
4. Positive Control	DNCB	DNCB	-	3/sex
5. DNCB Vehicle Control	80% Ethanol	DNCB	-	3/sex

Results: One f in group 5 died 10 days after the last induction exposure and the cause of

