RECOMMENDATIONS:
This product is approvable provided the applicant submits labeling consistent with the attached draft labeling.

/S/
John E. Hyde, Ph.D., M.D. 12-29-98

Orig. NDA # 20-619
HFD-550/Div File
HFD-340
HFD-550/CSO/Lutwak
HFD-550/Chem/Yaciw
HFD-550/Pharm/Yang
HFD-725/Stat/Taneja
HFD-880/Biopharm/Wang
HFD-550/MO/Hyde/Fang

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-612

Hind Health Care, Inc.
Attention: Larry J. Caldwell
Consultant to Hind Health Care, Inc.
165 Gibraltar Court
Sunnyvale, California 94089

Dear Mr. Caldwell:

Please refer to your May 31, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidoderm Patch (lidocaine dermal patch).

We acknowledge your correspondence and submissions dated July 17, September 25, and October 9 and 16, 1996.

We have completed our review of this application, as amended, and find that the information presented is inadequate and that the application is not approvable at this time.

Under section 505(d) of the Act and 21 CFR 314.125(b)(5) of the FDA implementing regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Lidoderm Patch will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the application fails to contain adequate and well-controlled studies that show a clinically significant difference, between Lidoderm Patch and placebo patch for treatment of chronic pain of post-herpetic neuralgia.

The application also fails to contain adequate and well controlled studies which support the use of Lidoderm Patch for the relief of acute allodynia. The findings with respect to allodynia are confounded by the differences between Centers in the study, the failure to show any clinical significance of the measurements and the use of multiple secondary endpoints. Additionally, the findings have not been replicated in another study and were not defined as primary endpoints in the one study in which it was measured.

Under section 505(d) of the Act and 21 CFR 314.125(b)(1) of the FDA implementing regulations, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. Specific deficiencies have been summarized below:

1. The limits and tests for impurities, degradants, and microbial limits in the drug product have not been specified. The limits set should be based on the manufacturing experience.

2. The 2,6-xylidine specification and test method are not acceptable. Specificially:

   a) A specification set at the method's detection limit is not acceptable. The specification should be well within the detection limit.

   b) The difference between the sample concentration and the standard concentrations is too wide a disparity (μg/mL).

   c) The method's validation with concentrations of 2,6-xylidine higher than those routinely observed in the drug product does not provide adequate support of the method's suitability for the 2,6-xylidine concentrations normally present in the drug product.

   d) Data are not provided to show that the proposed extraction procedure is capable of extracting 2,6-xylidine present in the drug product.

   e) There is a discrepancy between the reported value for the lower limit of detection. In one location it is listed as 0.1% (or 0.7 mg/patch) and in the stability data on the following page it is reported to be 0.150-0.341 mg/patch. This should be clarified.

3. Specifications and justification of the upper and lower limits for the adhesive strength testing have not been adequately provided. Please supply information to support a correlation between the proposed specification for the patch (i.e., retards a steel ball for 5 seconds) and the patch's ability to adhere to skin. Please submit an upper limit and include the justification for the value and test selected. All results of testing should include the specific time of retardation, not simply "conforming."

4. The assay validation data for pharmacokinetic study were not included in this application. Please submit a full assay validation report to the Agency.

5. The Environmental Assessment (EA) is inadequate. Specifically:

a) is the supplier of the lidocaine drug substance and not the manufacturer. Please replace all references to this company with the pertinent data for the drug substance manufacturer.

b) Please provide the CAS numbers for the additives, preferably in tabular format. The monographs are not necessary, but if provided, they should be from United States Pharmacopeia (USP) 23 and not USP 22.

c) A certificate of compliance should be submitted for the drug substance manufacturer. See section VI of the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements.*

Although not the basis for not approving this application, we have the following comments and requests for information that should be addressed:

3. The manufacturing batch record for Step on page 154, is unclear with respect to the following:

4. Please clarify what is meant by "Not Dissolution" on page 157 under Waste Amount.

5. The use of USP as a method identification in the specifications sheet is inappropriate because it incorrectly implies the existence of a USP monograph for this product.

6. The drug product specifications, methods and their justification documents should be based on the amount of drug per patch and not per gram of adhesive. Please provide revised applicable documents reflecting this change.

7. The information submitted for the procedures used for the drug product are not adequate:

   a) The preparation of the mobile phases is not clear. Please clarify the order in which the modifiers, water, and organic solvents are mixed.

   b) The resolution parameters for the procedures should be more specific. Stating that the resolution is "complete" is not sufficient. Please refer to USP general chapter <621> for guidance.

   c) Some of the monograph procedures and their justification documents are inconsistent with regard to the method's sensitivity measurement. The monograph procedures require the standard peak height to be exact whereas the justification document allows it to be "about" that height. Please clarify.

8. The basic procedure for the "recovery test" in the justification documents, i.e., adding a solution onto patch pieces and then extract with the same or similar solvent, is not a valid measure of the extraction of components of the patch. Please provide an acceptable "recovery test". Please also provide data for the extraction of the components from the patches reported in the recovery test.

9. Please provide the complete composition of the felt backing material and release liner material. The pouch laminate specifications and release liner testing should include a specific identification test for the plastics used.

10. The stability commitment dated July 2, 1996, is incomplete. It should include testing of one batch of the drug product per year in addition to the initial testing of the first three production batches. Please provide the revised stability commitment.

11. The stability study samples should be stored under controlled temperature and relative humidity (RH) conditions. The recommended storage conditions are 25°C/40% RH and 40°C/20% RH. Please submit a revised stability protocol reflecting these conditions.

12. The drug release test listed in the proposed stability protocol should be performed at each time point (controlled room temperature conditions and accelerated conditions).

13. The Methods Validation Package submitted was incomplete. Please resubmit a Methods Validation Package containing the following information:

    a) A tabular list describing all of the samples to be provided, including standards and internal standards that are not readily available, and their batch number and amount.

    b) Complete test results for all samples to be provided.

    c) A copy of all proposed regulatory specifications and methods.

    d) Information supporting the integrity of the reference standards and their ability to serve their intended purpose.

    e) Statement of the composition of the finished dosage form.

    f) Information supporting the suitability of the proposed methodology for the dosage form.

    g) System suitability tests for all procedures and others where appropriate.

h) A summary of developmental data to demonstrate each method's precision, linearity, accuracy, sensitivity, and specificity for the intended assay.

i) Material Data Safety Sheet or equivalent information (29 CFR 1910.1200), where appropriate, for any substance that will be supplied to FDA laboratories.

14. There is no means to identify the patch once it is removed from the envelope. Please provide a means of patch identification. If ink is used, please provide data demonstrating the ink's compatibility with the drug product.

15. The number of patches to be supplied in each envelope is not clear. The batches reported in the stability section and the September 25, 1996, amendment state five patches per envelope. The label states six patches per envelope.

16. Adequate identification of manufactured batches has not been submitted. Assigning one lot number to several batches of patches manufactured in a day is not acceptable. Each batch of patches should have a distinct identification (lot) number.

17. Analytical results should be reported in the same units as those stated in the specification.

18. Please use only one page numbering system in future submissions.

19. In the section of "Overall Summary - Pharmacokinetics" reference is made to pharmacokinetic data collected in Phase 2 and 3. Please submit these reports.

20. Please submit *in vitro* release methods to determine the drug release rate through a membrane. Such method should be able to differentiate between lots of manufactured product on the basis of drug release and should serve as a specification for quality control .

21. All references to the USP should be to USP 23 or the current USP.

Any resubmission of this application should also include an updated safety report as specified under 21 CFR 314.50(d)(5)(vi)(b).

We reserve comment on the proposed labeling for this product, until the application is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

Should you have any questions please contact Chin Koerner, Project Manager at 301-827-2090.

Sincerely,

Wiley A. Chambers, M.D.
Acting Director Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD 550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: NDA 20-612
HFD-105
HFD-550
HFD-550/Chambers
HFD-550/Medical TL/Hyde
HFD-550/Pharmacology/Yang/3-24-97
HFD-830/Chemistry/Yaciw/3-28-97
HFD-550/Statistics/Stein/3-24-97
HFD-880/Pharmocokinetics/Wang
HFD-550/ Koerner
HFD-830/Chen
HFD-80
HFD-101/Carter

DISTRICT OFFICE

drafted: CCK/3/21/97
Final: Chambers 4/13/97 saved as N20612.7na

NOT APPROVABLE (NA)

9, 1

NOV 1 1998

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/02/98

FROM: Charlotte Yaciw, Chemist, HFD-830/550

THROUGH: Hasmukh Patel, Team Leader, HFD-550 HB 11/98

TO: Vickey Lutwak, Project Manager, HFD-550

SUBJECT: NDA 20-612, Amendment dated 10/21/98

This amendment responds to the Division's request that an upper limit be set for adhesive strength. The applicant has agreed and has provided a specification and test procedure. This limit is not currently supported by data, however, it will be acceptable if the applicant commits to

1) collect quantitative data from the upper limit testing, i.e., actual residence times, and
2) revise the upper limit criterion in accordance with the data

cc:
NDA 20-612
HFD-550/Division Files
HFD-550/PM/VLutwak
HFD-550/Chem/CYaciw
HFD-830/DNDCIII/CWChen

Document ID: n20612mem.doc

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/18/98

FROM: Charlotte Yaciw, Chemist, HFD-830/550 CYaciw

THROUGH: Hasmukh Patel, Team Leader, HFD-550 HMP 11-20-98

TO: Vickey Lutwak, Project Manager, HFD-550

SUBJECT: NDA 20-612, Amendment dated 11/6/98

This amendment agrees to the following:

1) collect quantitative data from the upper limit testing, i.e., actual residence times, and
2) revise the upper limit criterion in accordance with the data

The amendment also includes updated carton labeling incorporating the standard storage statement.

This is acceptable. The CMC section is now in APPROVE status.

cc:
NDA 20-612
HFD-550/Division Files
HFD-550/PM/VLutwak
HFD-550/Chem/CYaciw
HFD-830/DNDCIII/CWChen

Document ID: n20612mem2.doc

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 11, 1999

FROM: Hasmukh B. Patel, Ph.D., Chemistry Team Leader, HFD-550 HBP 3-12-99

THROUGH: Chi-Wan Chen, Ph.D., Director, DNDC III, HFD-830 CWC 3/15/99

TO: Vickey Lutwak, Project Manager, HFD-550

SUBJECT: NDA 20-612, Amendments dated February 9, 1999 and March 4, 1999

This amendment contains printed labels for Lidoderm Patch 5% envelopes (for commercial use and samples to doctors) and cartons. See attached copies of the labels. The labels submitted in these amendments differ from those submitted in the August 4, 1998 amendment with respect to the following:

a. Name of the "Manufactured for" (Endo Pharmaceuticals)
b. Names of preservatives in the drug product composition: not included
c. "Directions for use" in the carton labels: not included
d. Changed TM to ®

Except the names of preservatives in the drug product composition, the above changes are acceptable. Each carton contains six envelopes and each envelope label contains directions for use. According to Marina Chang, primary reviewer for the original labeling in this NDA, this is acceptable. In the opinion of this reviewer, the labels for both envelopes and cartons should include names of the preservatives present in the drug product. Dr. John Hyde (Deputy Director for Anti-Inflammatory and Analgesic products, HFD-550) concurred with it.

The NDA is recommended for approval provided the applicant agrees to include names of the preservatives present in the drug product in the labels for envelopes and cartons.

cc:
NDA 20-612
HFD-550/Division Files
HFD-550/PM/VLutwak
HFD-550/CFang/JHyde
HFD-550/Chem/CYaciw/HPatel
HFD-830/DNDCIII/BDunn/CWChen