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APPLICATION NUMBER:

20-947

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-947

Dimethaid International, Inc.
2220 Chalkwell Dr.
Midlothian, VA 23113-3884

Attention: Frederick Ballantyne, M.D.
Director, Clinical Research and Regulatory Affairs

Dear Dr. Ballantyne:

Please refer to your December 15, 1997, new drug application (NDA) which was withdrawn October 26, 1998, and resubmitted August 7, 2001, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (diclofenac sodium topical solution) 1.5% w/w.

We acknowledge receipt of your submissions dated January 8 and 14, March 26 and 31, April 7 and 29, July 31, and October 26, 1998, August 7, September 20, October 5, and December 3, 2001, February 13, March 28, April 3, May 7 and 8, June 28, July 26, September 24, and November 7, 2002, October 6, 2003, and June 28, August 17, September 18 and 29, October 11, 12, 13, 23, 25, 26, and 27, and November 8, 10, and 15, 2006.

Your submission dated June 28, 2006, constituted a complete response to our August 7, 2002, action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

1. Demonstrate that the DMSO component of the product does not, through its solubilizing properties, result in excessive exposure to likely environmental toxins and microbiological agents (e.g., DEET, sunscreen active components), and/or provide data to define a time period after product application during which patients must avoid these exposures and that can be appropriately addressed in the product labeling.
2. Assess the toxicological potential of PENNSAID® in repeat-dose dermal toxicology studies because of the potentially high level of absorption of the product components due to the DMSO and because DMSO is considered a novel topical excipient due to its high concentration.
3. Limit the _____ impurity, which contains a structural alert, to NMT _____ micrograms total daily intake. Therefore, tighten the acceptance criterion for this _____ impurity to NMT _____ in the drug product or characterize its genotoxic potential in a minimal genetic toxicology screen.

b(4)

4. Limit the extractables from the HDPE bottles according to Agency guidelines or provide appropriate toxicological qualification of these impurities.
5. Switch all packaging from _____ to HDPE bottles, after addressing the toxicological potential of the extractables from the HDPE bottles as noted above.
6. Characterize the carcinogenic potential of PENNSAID® via dermal carcinogenicity studies, or provide an adequate scientific rationale for why such information is not necessary for the safe use of the product.
7. Conduct appropriate photostability studies to assess the potential for photodegradation impurities, and characterize the toxicity of any impurities found in these studies if above the qualification threshold described by ICH Q3b guidelines.

b(4)

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. **Include an integrated safety dataset from all Phase 3 clinical trials. The variable names in the datasets should be kept consistent across trials.**

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment 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), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport

12/28/2006 04:32:49 PM



NDA 20-947

Dimethaid Research, Inc.
Attention: Dr. Frederick N. Ballantyne
10455 North Central Expressway
Suite 109 PMB 320
Dallas, Texas 75231-2213

Dear Dr. Ballantyne:

Please refer to your new drug application (NDA) dated August 7, 2001, received August 8, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pennsaid (diclofenac sodium) Topical Solution 1.5% w/w.

We acknowledge receipt of your submissions dated September 20, and October 5, 2001, February 13, March 28, April 3, May 7, May 8, and June 28, 2002.

You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review and find the information presented is insufficient to determine if the drug is safe and effective under the proposed conditions of use. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Clinical Deficiencies:

Efficacy:

There is insufficient information to conclude that Pennsaid applied topically to a knee is efficacious for that particular knee. Demonstration of efficacy at the site of application is critical for approval of a topical formulation.

In both pivotal Studies 109 and 109-US, the compassionate use of therapy was extremely high. This confounds analysis of the data. Therefore, in an attempt to understand the data as well as possible, the Division reanalyzed the data with patients being assigned into one of three treatment categories. Category 1 patients had the target knee-only treated during the entire study. Category 2 patients had the target and non-target knee treated during the entire study. Category 3 patients had the target knee treated during the entire study, but also may have treated their non-

target knee during some portion of the study. Of the number of Intent to Treat (ITT) patients for Study 109 and 109-US combined (536 patients), the following number of patients were included in Categories 1, 2, and 3, respectively: 111 (21% of total), 348 (65% of total), and 77 (14% of total).

Such a large extent of contralateral use confounds the analysis of efficacy of a topical therapy. There was no prespecified stratification of patients into these three treatment arms; patients were allowed to apply treatment to more than one knee based on a "compassionate" basis. Therefore, the effects of randomization in any subanalysis based on category were lost.

Only in Category 2 (both knees treated during the entire study) was there a statistical support for efficacy for the three co-primary endpoints. In Category 2, the trends were inconsistent.

Efficacy must be demonstrated in the three co-primary endpoints of pain (WOMAC pain subscale), function (WOMAC function subscale) and patient global. The results for Pennsaid do not demonstrate efficacy in the Category 1 and 3 patients. In the Category 2 patients, only a single knee was analyzed for efficacy and so it is unknown if there was clinical benefit in the other treated knee.

The reanalysis of data, as described in the clinical efficacy section above, formed the basis for the statistical review of this NDA. This was because the primary analysis presented in the NDA excluded many randomized patients in Study 109 and 109-US. All randomized and treated patients are typically included in an ITT analyses. Several such analyses with different imputation methods for missing values were performed by the Division. These analyses show that, depending on the imputation method, the results of the NDA's primary analysis are reversible.

From a trial design point of view, there were no scheduled measurements made between baseline and final assessments from either Study 109 or 109-US. Measurements made in the early or the middle stages of a trial are considered important because they provide information about the time course of drug efficacy. For example, it is important to understand when an effect might begin and whether this effect is maintained, increased, or diminished by the end of study. Future studies should address these issues.

Safety:

Inadequate data was provided to demonstrate long-term safety for this drug product.

In addition, demonstration of safety in situations of co-administered therapies, which is likely to occur once a topical agent is approved, is needed. No safety information on the use of Pennsaid with daily oral anti-inflammatory and analgesic therapies was provided.

There are no clinical laboratory data and no data on co-administration with other drugs (except rescue acetaminophen) in either Study 109 or 109-US.

There are substantial differences in reporting of some adverse events (AEs) between Studies 109 and 109-US and other NDA studies. For example, arthralgia is listed to occur between 1.9-3.7% for the Pennsaid groups in Study 109 and 109-US, but 34.5% in Study 107-96.

Similarly, arthralgia was noted in 1.9-4.6% of patients treated with DMSO in Study 109 and 109-US, but in 40% of DMSO treated patients in Study 107-96. It is unclear why this difference exists. Since DMSO is an important component of Pennsaid, all AEs in these two groups in Study 109 and 109-US are considered to occur with Pennsaid. Therefore, there is no clear understanding of the adverse event profile of Pennsaid versus a "non-diclofenac" 45.5% DMSO-containing control.

Under ICH guidelines the Sponsor is required to submit safety data from the sample size of 300-600 patients treated for 6 months and from 100 patients treated for 12 months. You have submitted data from two open-label, long-term studies, EDR and 105-95.

There are no AEs reported for EDR. The rates of AEs in Study 105-95 are very low compared to controlled studies even for skin reactions that are very common with the use of this drug. This is suggestive of very significant underreporting and, therefore, cannot be viewed as adequate safety data for long-term use of the drug.

Because of the above deficiencies, the safety of Pennsaid has not been adequately demonstrated in this NDA.

Clinical Pharmacology/Biopharmaceutics Deficiencies:

Based on both the amount of diclofenac contained in this solution and the proposed conditions of use, no additional systemic pharmacokinetic information is needed relative to the diclofenac component of this product. However, you have not provided an adequate evaluation of the pharmacokinetics of DMSO following topical administration. As part of the clinical program for this product, you should undertake a study whereby both single dose and multiple dose pharmacokinetic sampling is undertaken for DMSO and its major metabolites with both an adequate number of samples and subjects. This study must be conducted prior to approval.

In order to address the issue of local (sub-stratum corneum) depot formation, you are encouraged to evaluate the uptake of DMSO and diclofenac into the different layers of skin using microdialysis.

Additional requests:

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Review of the literature and labels for DMSO, along with efficacy results for Study 102-93-1 and adverse events (i.e. paresthesia at site) in Study 107-96 suggest DMSO is an active component of Pennsaid. Therefore, Pennsaid may represent a combination product which will need to be studied as such in future trials.

2. Describe in detail any significant changes or findings in the safety profile.
3. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

Present tabulations of the new safety data combined with the original NDA data.

Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

4. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
5. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
6. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

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 your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment 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.

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The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, M.D.
Director
Division of Anti-Inflammatory, analgesic,
and Ophthalmic Drug Products
Office of Drug Evaluation ODE V
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Lee Simon

8/7/02 09:36:56 AM



DEC 16 1998

NDA 20-947

Dimethaid Research Inc
Attention: Zev Shainhouse, MD, BSc., FRCPC
Medical Director
1405 Denison Street
Markham, Ontario L3R 5V2

Dear Dr. Shainhouse:

As we agreed, here is a list of the medical and chemistry deficiencies to date for your new drug application (NDA) dated December 15, 1997, received January 8, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pennsaid (diclofenac sodium lotion) 1.5% and withdrawn on October 27, 1998. Please be advised that the NDA review was not completed, and the list could be amended with the discovery of new deficiencies after the NDA is resubmitted.

LIST OF DEFICIENCIES AND COMMENTS

MEDICAL

Study 102-93-1 does not provide substantial evidence of efficacy of Pennsaid, because the primary variable did not show a statistically significant difference between Pennsaid and control.

CHEMISTRY

Recently, our inspectors could not complete inspection of your manufacturing facilities for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. A satisfactory inspection will be required before this application may be approved.

Major deficiencies:

1. Please explain the excessively wide point-to-point variability of your stability data, especially the dimethyl sulfoxide (DMSO) assay, diclofenac sodium assay and diclofenac sodium impurity assay data. Do these data accurately reflect the behavior of the product over time? Do they indicate a problem with the analytical methodology?

2. There are no primary stability data for Pennsaid packaged in the 15 and ——— sizes, i.e., packaged in the container/closure systems described in this NDA. The stability reports submitted for these sizes indicate that they were packaged in ——— bottles. This does not match the container information provided in the NDA. **b(4)**
3. All stability reports must include the initial point data. Only one of the submitted 25°C reports contains these data.
4. The proposed “shelf life” impurity specifications for Pennsaid are set too high. Please submit impurity specifications which are justified by the stability data.
5. Please provide data showing that the proposed ——— container/closure system is chemically and physically compatible with the drug product. **b(4)**
6. Please provide data on the photostability of Pennsaid. This was requested at the pre-NDA meeting.
7. Please provide data for the Preparatory Testing section of the USP Microbial Limits chapter to show that the testing is valid for this product. This was requested at the pre-NDA meeting.

Other deficiencies:

8. A maximum mixing time should be established and validated for the dissolution of the diclofenac sodium ———). This was requested at the pre-NDA meeting. **b(4)**
9. A maximum hold time between the manufacture of the product (through ——— and filling into the bottles should be established and validated. This was requested at the pre-NDA meeting.
10. Please clarify whether the “Regulatory Specifications and Methods Used to Test Pennsaid After June 1, 1997” will be used as regulatory specifications for the post-approval testing of the product marketed in the US.
11. Please state the expected shelf life for each fill size.
12. Please clearly indicate the stability protocol which will be used for the post approval and annual batch studies.

13. The container labels should be revised as follows:
- a. The ethanol content must be stated (as w/w).
 - b. The _____ statement should be replaced with "Rx (or Rx) only".
 - c. The term _____ should be replaced with "Other".
 - d. The storage statement should be revised to read "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."
14. The package insert should be revised as follows:
- a. In the Description section, only one version of the chemical name is needed.
 - b. In the Description section, providing the amounts of each inactive component is optional.
 - c. In the How Supplied section, a brief description of the container should be provided, i.e., in _____ with dropper caps.
 - d. The storage statement should be revised to read "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."
 - e. The _____ statement should be replaced with "Rx (or Rx) only."

b(4)

b(4)

If you have any questions, contact Victoria Lutwak, Project Manager, at (301) 827-2090.

Sincerely,

JEH 12-16-98

John Hyde, Ph.D., MD
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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cc:

Archival NDA 20-947

HFD-550/Div. Files

HFD-550/Averbuch/Patel/Yaciw/Wang/Weir

HFD-550/CSO/Lutwak

HFD-725/Lin/Taneja

Drafted by: VL/November 1, 1998

final:

filename: 981101DE.WPD

Deficiencies