CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-029

Hisamitsu Pharmaceutical Co, Inc.
Attention: Cheryl D. Blume, Ph.D.
300 Campus Dr, Suite 220
Florham Park, NJ 07932

Dear Dr. Blume:

Please refer to your new drug application (NDA) dated February 27, 2006, received February 27, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Salonpas (1% methyl salicylate & 3% l-menthol) b(4)

We acknowledge receipt of your submissions dated May 15, June 8, 13, and 27, August 18 and 29, September 12, 25, and 27, October 12, and November 6, 2006.

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. Your single-patch study was not adequate to establish the dosing interval for your product, and thus cannot be labeled for consumer use. The data do not support use of a second dosing period over 24 hours. Therefore to address these concerns you must perform an adequate and well-controlled study to define the duration of effect and to demonstrate efficacy and safety over the proposed duration of use for which the patch will be labeled. b(4)

2. Once you have established the appropriate dosing interval, determine the safety profile for your product for its intended dosing schedule. To address this you will need to collect safety data in the multiple-dose efficacy study described above.

3. Provide an assessment of symptoms of excess systemic salicylate exposure at the recommended dosing regimen.

4. In view of the analytical assay methodology issues and the unreliability of the data submitted in the NDA, submit newly acquired pharmacokinetic data using adequately validated analytical assay methods. The new data should include the pharmacokinetics of methyl salicylate, salicylic acid, and l-menthol in male and female subjects dosed according to the proposed labeling. These data may be acquired from a stand alone pharmacokinetic study or from a subset of patients participating in a clinical study.

5. Low menthol and methyl salicylate assays were observed at 30 days when the pouch was not adequately closed. Therefore, revise your label to state that patches should be discarded 14 days after the pouch is opened.

In addition, it will be necessary for you to submit draft labeling revised as follows:

1. [redacted]

2. Your tradename "Salonpas [redacted]" is not an acceptable tradename and should be changed to your proposed tradename "Salonpas [redacted]" b(4)

These labeling comments are preliminary and additional revision of the labeling may be required based on your response to the deficiencies cited above.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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.

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:

   - 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 retabulated 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.

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 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 Division of Nonprescription Clinical Evaluation and the Division of Anesthesia, Analgesia, and Rheumatology Products 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 LCDR Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, MD
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Deputy 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/

Joel Schiffenbauer
12/27/2006 01:31:19 PM

Sharon Hertz
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