CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-623

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-623

Zars, Inc.
350 West 800 North, Suite 320
Salt Lake City, Ut 84103

Attention: T. Andrew Crockett
Clincal and Regulatory Affairs

Dear Mr. Crockett:

Please refer to your new drug application (NDA) dated March 31, 2003, received April 4, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg.

We acknowledge receipt of your submissions dated August 1, September 9 and 15, and December 29 and 30, 2003.

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. There are inadequate controls over the acceptance testing and retest intervals for the two drug substances, lidocaine and tetracaine, [redacted]

   a. Provide revised acceptance specifications for lidocaine, USP, with the following test attributes:

      1) [redacted]
      2) Water content by the Karl Fisher method
      3) Residual solvents
      4) Clarity and color of solution

   b. Provide revised acceptance specifications for tetracaine, USP, with the following test attributes:

      1) Specific ID test such as IR
      2) Impurities and degradation products in conformance with ICH Q3A
      3) Heavy metals
      4) Residual solvents

c. Provide retest intervals with justification for lidocaine and tetracaine.

2. There are inadequate controls over the acceptance testing for the raw materials and the components of the S-Caine Patch at Tapemark.

a. [redacted] data sheet lists critical physical parameters of the [redacted], but also includes a disclaimer that the data is presented without any guarantee, warranty, or responsibility of any kind, express or implied. Since the [redacted] acts both as a [redacted] its physical properties should be adequately ensured for its intended dual role. Therefore, provide a revised data sheet from [redacted] with adequate assurance of the physical quality attributes. Alternatively, provide revised specifications from Tapemark with these physical test attributes.

b. Provide revised specifications for [redacted] with the following tests:

1) A specific ID test such as [redacted] test
2) Assay based on actual testing at Tapemark

c. Provide a justification for the stated shelf life [redacted] for [redacted] solution and also describe the nature of the container-closure system in which this is stored.

d. The absorption capacity of [redacted] is listed as a reference property only and it is not listed under the product specifications. Since the absorption capacity is a critical quality attribute to ensure adequate absorption of [redacted] solution in the patch, this should be listed under specifications. Therefore, provide a revised specification sheet from [redacted] listing absorption capacity as a required specification.

e. Provide a letter of authorization from [redacted] to reference their DMF for the manufacture and controls for the [redacted] Alternatively, provide a description of the manufacturing process of this [redacted] and list all components.

f. Provide a description of the test method for the peelable heat seal test and clearly define the acceptance criterion for this test in the specifications.

g. Provide a letter of authorization from [redacted] to reference their DMF for the [redacted] Alternatively, provide a description of the manufacturing and controls for this film.

h. [redacted] certificate of analysis (COA) for the CHADD pods, provided on page 326/Vol. 3C of the NDA is inadequate. Provide a revised representative COA from [redacted] with the actual observed values of the test results for CHADD™ pods.

i. Provide a representative certificate of analysis for the iron powder from the vendor, [redacted], with particle size distribution test results.

j. Provide a revised specification for sodium chloride from [redacted] with specific ID tests for sodium and chloride, such as [redacted] precipitation test.

k. The description of the container closure system for CHADD heating pods is unclear as to how much protection the [redacted] would provide to the CHADD pods against [redacted] the anticipated duration of storage of CHADD pods.

3. The acceptance testing criteria and the impact of the hold time of S-Caine bulk material on the expiration dating of the S-Caine Patch are not described clearly and adequately.

   a. Provide a description of [redacted] on quantitation of syneresis and the acceptance criteria for the extent of syneresis if observed in the visual inspection of S-Caine bulk material.

   b. Tapemark's practice of sending the S-Caine bulk material back to [redacted] for the ID testing is unacceptable. Provide revised specifications for the S-Caine bulk material stating that the ID testing will be carried out by an independent testing laboratory.

   c. Tapemark's designation of [redacted] period from the date of manufacture of S-Caine bulk material would imply that the material might continue to be stored beyond [redacted] as long as retest results conform to the specifications. Since this practice is unacceptable, provide a revised statement identifying the maximum hold time with justification.

   d. The expiration dating should commence from the date when the drug substance is mixed with other excipients. Therefore, provide a statement that the expiration dating for the drug product, S-Caine Patch, would be computed from the date of manufacture of the S-Caine bulk material.

   e. Provide a revised specification sheet for the S-Caine bulk material with viscosity testing as part of the release and stability testing. Alternatively, justify why viscosity measurement is irrelevant for ensuring the physical integrity of the emulsion form of the bulk material.

4. Manufacturing batch records and process controls for the S-Caine Patch should be revised to reflect the process used to manufacture the product used in the pivotal clinical studies, and to produce the drug product consistently:

   a. Note that the revised master production batch record submitted on December 30, 2003, is the official batch record for commercial production, since this reflects more accurately the executed batch records of the primary NDA batches used in the pivotal clinical studies and stability studies. Proposed changes in the heat sealing process and other manufacturing changes should be submitted with comparative stability data for the patches made with the current and the revised processes.

b. Provide the following additional in-process controls in the heat sealing operations of the [redacted] and of the [redacted] pouch during the manufacture of the S-Caine Patch:

1) [redacted]
2) [redacted]

c. The test frequency of the in-process testing in the manufacture of the S-Caine Patch including packaging operations [redacted]

5. The drug product specifications need to be revised to reflect the desired product performance. Some of the analytical methods need to be refined for better control.

a. Provide additional system suitability criteria, namely the tailing factors and theoretical plates in the assay methods STM 04-104 and 04-103, for the determination of lidocaine, tetracaine, methylparaben, and propylparaben.

b. The HPLC based ID test is not a specific ID test for lidocaine and tetracaine. Provide an additional non-specific test such as UV or colorimetry or a specific ID test such as IR for the drug product.

c. Being a rat carcinogen, [redacted] should be tightened to as low levels as achievable. Therefore, provide revised drug product specifications with a limit of NMT for this degradant in the drug product.

d. The acceptance criterion for the temperature test is inadequate to ensure proper heating of the patch and heat-activated drug release for enhanced efficacy. For example, clinical study SC-27-01 did not show significant effect of heating versus not heating the patch on efficacy. In light of this, revise the acceptance criteria by tightening the average lower ranges to e.g. [redacted] and provide ranges for individual heating pods with justification. Alternatively, provide adequate justification to the contrary.

e. Provide data on the temperature ramp profile of the heating pods used in the Phase 3 studies, describing the rate of increase in the temperature with time from T = 0 until it reached its maximum.

f. The actual temperatures achieved in the pivotal clinical studies by the CHADD heating pod were in the range [redacted], however, the drug release testing was carried out at 40°C. Reconcile this discrepancy and justify why conventional temperature of 32°C was not deemed appropriate for this test.

g. Justify why [redacted] was used as [redacted] in the drug release test media.

h. The procedure followed in proposing the acceptance criteria for the drug release is based on the mean $\pm$ 3 σ and is not considered suitable for this type of test. In the absence of a meaningful link to and support from bio-studies, the acceptance criteria should not be wider than $\pm$ 10% (absolute) around the mean. Moreover, three levels of testing are permissible in USP<724> and they provide for additional allowances for wider individual ranges. Therefore, provide the following tighter acceptance criteria for the drug release for both lidocaine and tetracaine:

1) 20 min: [redacted] LC for both lidocaine and tetracaine
2) 40 min: [redacted] LC for both lidocaine and tetracaine
3) 60 min: Not Less Than [redacted] LC for lidocaine and NLT [redacted] LC for tetracaine.

6. Significant stability trends were noted in the primary stability study presented in the NDA. Of concern were the tetracaine assay and its degradation products, and the *in vitro* drug release.

a. The *in vitro* drug release rate declined significantly in the stability studies, for both lidocaine and tetracaine. Although this test is being proposed as a quality control tool without any correlation with the *in vivo* performance, the declining trend in the drug release is of concern, as it is likely to impact the *in vivo* performance. Therefore, provide a breakdown of the age of the patch used in the pivotal clinical studies and the instances of patch failure due to ineffective anesthesia, if observed in the clinical studies. Also clearly identify the patients treated with the patches that were close to the proposed expiration dating of 18 months.

b. The proposed range for the adhesion strength should be supported by the data from the product used in the clinical studies. Therefore, provide data indicating whether there was a correlation between the age of the patches used in the Phase III studies and their adhesion strength versus skin adhesion problems (peeling) and inadequate patient anesthesia, if observed.

c. The observed decrease in the drug release rate over storage seems to be related to the gel hardening due to aging. If this is confirmed, the gel hardening might lead to flake and powder formation and, hence, result in the drug availability when the release liner is removed before patch application. Provide data indicating instances of such observations in the aged patches that were at the near end of the proposed expiration dating of eighteen months.

7. Accidental mishandling of the patch is likely to release the iron powder, and, if it is exposed to air, it may rapidly heat up and cause thermal injuries. Provide data indicating whether S-Caine Patch can release the iron powder, and, if so, indicate the rate and extent of heating.

8. [redacted] referenced in support of tetracaine was deemed inadequate to support this NDA. A deficiency letter was sent to the DMF holder, [redacted]

9. Safety and efficacy data in pediatric patients less than 4 months of age is not provided. Provide a progress update for your proposed neonatal stud(ies), along with a timeline for enrollment, completion, and submission of the final study report. While it may be possible to extrapolate efficacy to this age group, efficacy endpoints should still be assessed in neonates.

10. Assessment of cumulative irritation and sensitization potential, as provided in the study report of SC-42-03, was not adequate for full review. It is not possible to ascertain the reasons for study drop-out in SC-42-03, and a full protocol was not provided. Submit a complete study report (with full CRFs for all study drop-outs, and for subjects that experienced AEs) for study SC-42-03. The report must also include complete documentation of the original protocol, protocol revisions, and study conduct.

11. As discussed during the pre-NDA meeting on December 5, 2002, submit the completed Segment I and Segment III reproduction studies on tetracaine to the S-Caine Patch NDA as soon as they are available.

12. The referenced reproductive toxicology literature you provided as adequate characterization of the effects of lidocaine on the fertility and early embryonic development is inadequate. For resubmission, you will need to provide data (original or public domain) that characterizes the effects of lidocaine treatment of the male on fertility and early embryonic development. Males should be treated daily for at least 4 weeks prior to mating, through gestation until termination of the males. You should provide data that characterizes the effects of lidocaine treatment each of the following endpoints:

    - Maturation of gametes
    - Mating behavior
    - Fertility
    - Sperm counts in epididymides or testes
    - Sperm viability, motility and morphology
    - Histopathology of male reproductive organs (epididymis, testis, seminiferous tubules).

The following preliminary comments pertain to the labeling. Additional comments will be provided once the aforementioned deficiencies are addressed.

1. Include revisions to the package insert, as indicated in the attached, edited document. Note that these revisions are only preliminary draft comments. Also, address the following recommendations.
    a. Rewrite the CLINICAL STUDIES section of the package insert to adequately reflect the clinical trials that support the final drug product.
    b. In the Handling and Disposal section, provide detailed instructions of how to properly dispose of the patch to prevent a child from inappropriately applying the patch to their skin (e.g., fold the sticky surface of the patch together, flush the patch down the toilet or etc.).
2. Submit images of the outer surface of the patch. The outer surface of the patch should present the proprietary name, established name and product strength.
3. Because the product contains iron powder, unless it is determined that the product can be safely worn during a MRI procedure, the labels and labeling should include a warning statement

4. The established name should contain the names of the drugs, the dosage form and the route of administration, where appropriate. The drug strengths are not part of the established names. Therefore, the following established name should be used in conjunction with the trade name.

   "S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg"

5. Include revisions to the container-closure system labeling as follows:

   a. Replace the descriptor [redacted] with the descriptor "For Local Dermal Analgesia."

   b. Increase the prominence of the established name to at least ½ the size of the proprietary name.

   c. Minimize the prominence of the company name at least to the level of prominence of the trade name.

   d. The Usual Dosage statement should begin with the phrase "Usual Dosage," and provide complete directions for use, which should include the duration of use.

   e. A route of administration statement similar to "For Topical Use Only" should be clearly presented on the labeling.

   f. Increase the prominence of the "Rx only" statement.

   g. The net quantity statement appears to be disjoined and separated by color and the use of different sizes of print. Presenting the net quantity statement without any distracting colors, images or differences in font style or print size that could confuse the reader.

6. Include revisions to the carton labeling consistent with any applicable comments above.

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

During a recent inspection of the manufacturing facilities for this application, our field investigator conveyed deficiencies to the facilities' representatives. Satisfactory resolution to these deficiencies is required before this application may be approved.

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.

In addition, we have the following comments which are not approveability-related, however, response to them is requested.

1. The pharmaceutical development section was inadequately described and clear reasoning for the formulation changes and the utility and the role of the patch components in patch performance were not presented.

   a. Your justification for a change in the formulation from developmental formulations A and B to the final formulation indicates that the changes were made to [redacted] of the product. However, due to [redacted] in the patch in the final formulation, increased skin absorption is also a possibility. Therefore, provide the following data.

      1) Data supporting [redacted] of the final formulation.
      2) Impact of the formulation change on the skin absorption of the drugs.

   b. Provide a clear rationale for the utility of [redacted] film in the drug product, which is identified as a [redacted] Provide data indicating whether the patch can still perform without this component or not.

2. You are strongly encouraged to study the efficacy of S-Caine in procedures other than venipuncture or intravenous access in all pediatric age groups.

3. Although Geriatric trials demonstrated a statistically significant difference in primary endpoints between the S-Caine Patch and placebo, the magnitude of difference was small, and the secondary endpoints fail to support the clinical significance of these differences. You are strongly encouraged to provide additional geriatric efficacy data to define appropriate use of this product in geriatric patients.

4. [redacted]

5. The S-Caine heating element has not been demonstrated to contribute to product efficacy. Provide evidence that the heating element contributes to the patch, along with appropriate CMC specifications. Alternatively, the product will be labeled to state that the heating element is ineffective, and CMC specifications must be appropriate to ensure that the heat generated may not impact on product safety (e.g. time profile of warming, temperature range and max).

6. Clarify the equivocal finding in the *in vitro* chromosomal aberrations assay for tetracaine. This clarification could take the form of a direct repeat of the assay with examination of the in vitro culture conditions such as pH or osmolarity changes which may contribute to a positive result. The clarification should be included with the complete response.

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 an informal 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 Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

15 Page(s) Withheld

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/s/

Bob Rappaport
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