

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-516

Approvable Letter (S)



NDA 21-516

Senju Pharmaceutical Co., Ltd.
c/o Ista Pharmaceuticals, Inc.
Attention: Marvin J. Garrett
Vice President
15279 Alton Parkway, Suite 100
Irvine, California 92618

Dear Mr. Garrett:

Please refer to your new drug application (NDA) dated September 25, 2002, received September 26, 2002, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Istalol (timolol maleate ophthalmic solution) 0.5%

We acknowledge receipt of your submissions dated November 11 and December 16 (two), and 17, 2002, and January 9, 10, 22, and 23, February 14 and 18, April 4, 11, and 23, May 21, and July 9 and 18, 2003.

We also acknowledge receipt of your submissions dated May 30 and June 5 (two), 16, and 23, 2003. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We 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. The controls used for the manufacture, processing, packing, or holding of the drug substance are inadequate to preserve its identity, strength, quality, purity, and stability. The drug substance specification should be revised to include the individual residual solvents.
2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product are inadequate to preserve its identity, strength, quality, purity, and stability.
 - a) Provide the [] the critical manufacturing area.
 - b) Provide the [] limits for the []
 - c) The [] holding times and the [] bioburden limit should be provided even though the product contains a preservative. Actions taken when this limit is exceeded should also be provided.

- d) Provide [] cycles listed (Volume 5, p. 16).
- e) With regard to [] equipment:
- i. Describe how the validation runs conducted []
Please note that [] validations should be conducted.
 - ii. Provide the manufacturer, []
 - iii. Indicate the differences []
- f) Regarding [] for the container/closure system:
- i. If [] other than the two described in attachment I (Volume 5, p. 94) will be used [], these should be specified. Please provide a summary of the number and types of components []
 - ii. Provide the frequency with which the component bioburden is checked []
- g) Regarding media fills:
- i. Provide the results of environmental monitoring conducted during the three media fills summarized in attachment J (Volume 5, p. 111).
 - ii. The media should be tested to insure its ability to support microbial growth. Please provide the media control data for these three media fills.
 - iii. Per Volume 5, p. 19, all of the media fills [] The summary of batch # 11111 (Volume 5, p. 112) states that although [] were filled, only [] were [] Please explain this discrepancy.
- h) Please provide the frequency and locations of WFI sampling.
- i) Regarding the container/closure integrity test:
- i. Please clarify how []
 - ii. Integrity testing should be conducted with container components []
- j) Total manufacturing times [] should be listed in the master batch record. Please submit the revised master batch record.

k) Regarding the drug product specification:

- i. For identification test, one specific test or two non-specific tests should be included.
 - ii. The proposed acceptance criterion of NMT [] for the unknown degradation products [] at the shelf-life is not acceptable. Based on data, the acceptance criteria for these degradation products should be NMT []. The acceptance criterion for the total impurities should also be tightened to reflect actual data. In addition, a new entry for "any unspecified impurity" with acceptance criterion of NMT [] should be included.
 - iii. Submit the [] test.
- l) Include a limit of quantitation at [] as part of the system suitability test for the HPLC method # [] (assay/impurity).
 - m) The proposed container closure system [] LDPE bottle has not been supported by adequate stability data. According to the ICH Q1A guidance, stability data from 3 primary batches of the drug product proposed for marketing should be provided at NDA submission.
 - n) The anticipated number of commercial batches of the drug product expected to be produced per year should be stated. The expected introduction concentration (EIC) of the drug substance at the point of entry into the aquatic environment should be provided.
 - o) During a recent inspection of the drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the facility's representative. Satisfactory resolution to these deficiencies is required before this application may be approved.

Although not required for the approval of this application, please provide the duration of treatment (i.e. number of study days until advent of adverse event) for each subject with an adverse event through Month 12 in TIMLA-301.

We will continue to work with you on the proposed labeling.

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.

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 Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
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/

Wiley Chambers
7/25/03 03:32:54 PM