

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-516

Administrative/Correspondence Reviews

EXCLUSIVITY SUMMARY FOR NDA # 21-516 SUPPL # _____

Trade Name Istalol

Generic Name timolol maleate ophthalmic solution 0.5%

Applicant Name Senju Pharmaceutical Co., Ltd HFD # 550

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / X / NO / ___ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / ___ / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-086 Timoptic

NDA# 19-463 Timoptic in Ocudose _____

NDA# 20-330 Timoptic XE _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__ / NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b) (2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__ / NO /__ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__ / NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__ / NO /__ /

If yes, explain:

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

See electronic signature page

William M. Boyd, M.D.
Medical Officer

Wiley Chambers, M.D.
Deputy Division Director

Cc:

Form OGD-011347 Revised 05/10/2004

**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
6/4/04 06:47:38 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-516

Stamp Date: September 26, 2002 Action Date: June 4, 2004

HFD-550 Trade and generic names/dosage form: Istalol (timolol maleate ophthalmic solution) 0.5%

Applicant: Senju Pharmaceutical Co., Ltd. Therapeutic Class: 3 - New Formulation

Indication(s) previously approved: None

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied for pediatric population

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

NDA 21-516
Page 2

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

Products in this class for this indication have been studied for pediatric population

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Michael Puglisi
Consumer Safety Officer

cc: NDA 21-516
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Michael Puglisi
6/7/04 11:55:44 AM

Memo

To: Brian Harvey, M.D., Ph.D.
Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Through: Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

CC: Mike Puglisi
Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

Date: May 13, 2004

Re: ODS Consult 02-0218-1 Istalol (Timolol Maleate Ophthalmic Solution) 0.5%; NDA 21-516.

This memorandum is in response to a April 14, 2004, request from your Division for a re-review of the proprietary name, Istalol. Container label as well as carton and insert labeling were submitted for review and comment.

Since the time of our initial review, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Istalol. DMETS initially reviewed the proprietary name Istalol on June 6, 2003 (see ODS consult 02-0218-1) and did not recommend its use due to look-alike and/or sound-alike similarities with the currently marketed products Stadol, Esmolol, and Sotalol. DMETS still believes that these names pose a potential for confusion and continues to not recommend the use of the name Istalol.

In the review of the draft container labels as well as the insert and patient labeling of Istalol, DMETS has focused on safety issues relating to possible medication errors, and has identified one area of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

Increase the prominence of the statement "For topical application in the eye" and relocate to main display panel.

B. CARTON LABELING

1. See comment under CONTAINER LABEL.
2. The vertical presentation of the name "Istalol" on the carton labeling may cause confusion especially since the distributor's name "ISTA" is cited horizontally at the top. The proprietary name, established name and strength should be presented horizontally and the distributor's name should be relocated to the bottom or side panel.

C. PACKAGE INSERT

Revise the abbreviation "AM" to read "morning" to avoid any confusion and possible error.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

**Appears This Way
On Original**

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

/s/

Alina Mahmud
5/14/04 03:06:50 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/14/04 03:12:57 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-516

4/12/04

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 the teleconference between representatives of your firm and FDA on April 5, 2004. The purpose of the meeting was to provide Agency guidance concerning the labeling for Istalol (timolol maleate ophthalmic solution) 0.5%.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure



MEMORANDUM OF TELECONFERENCE MINUTES

TELECONFERENCE DATE: April 5, 2004
START TIME: 3:00 pm

APPLICATION (DRUG): NDA 21-516
Istalol (timolol maleate ophthalmic solution) 0.5%

SPONSOR: Senju Pharmaceutical Co., Ltd

TYPE OF MEETING: Guidance

MEETING CHAIR: Wiley A. Chambers, MD

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS:

Wiley Chambers/ Deputy Division Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Lucious Lim/ Medical Officer
Rhea Lloyd/ Medical Officer
Martin Nevitt/ Medical Officer
Dennis Bashaw/ PK Team Leader
Linda Ng/ Chemistry Team Leader
H. Shawn Khorshidi/ Chemistry Reviewer
Carmen DeBellis/ Chief Project Manager
Michael Puglisi/ Project Manager
Lori Gorski/ Project Manager
Raphael Rodriguez/ Project Manager

INDUSTRY PARTICIPANTS:

Marvin Garrett/ V.P., Reg. Affairs, Quality, and Compliance
Paul Krause/ Director, Regulatory Affairs
J Consultant
Kirk McMullin/ Vice President, Operations
Steve Massah/ Manufacturing Support and Technology Transfer
Tom Mitro/ Vice President, Sales and Marketing

MEETING BACKGROUND:

The Agency sent revised package insert labeling for this original NDA to the Sponsor in a March 8, 2004, fax. On March 12, 2004, the Sponsor submitted a request for a teleconference with a list of questions and comments concerning the Agency's changes to the label. The Sponsor submitted a March 19, 2004, amendment with questions concerning carton and container labeling. The Agency provided written responses to the Sponsor's questions in an April 2, 2004, fax. The Sponsor responded in an amendment dated April 2, 2004. This teleconference served to address the remaining unresolved labeling issues for this product. The following shows the rounds of Agency and Sponsor comments, including those conveyed in this teleconference:

Package Insert

Original ISTA Question #3 - Under Clinical Pharmacology, Pharmacokinetics, we believe the two paragraphs on rabbit studies that have been deleted provide useful information and should remain in the package insert text. Would it be acceptable to keep these paragraphs if we add a new heading ☐

Original FDA Response: *No. Disagree that these two paragraphs on animal studies have clinical relevance.*

ISTA Response: By including a brief description of the referenced animal studies showing enhanced absorption of timolol, our intention was to help prescribers understand why ISTALOL is administered once a day rather than twice a day. The referenced studies help explain why this is the case and are supported by the clinical studies submitted in the NDA.

Numerous ophthalmic products have animal studies or *in vitro* studies cited in the package inserts to explain the reasons the products work as indicated. For example, Alomide 0.1% (lodoxamide tromethamine ophthalmic solution), Alcon is indicated for treatment of allergic conditions of vernal conjunctivitis as a mast cell stabilizer. The agency allowed reference in the labeling to an *in vitro* study that "demonstrates the ability of lodoxamide to stabilize mast cells and prevent mast cell release." The reference is the PDR for Ophthalmic Medicines, 29th Ed., 2001, page 208

Natacyn (natamycin ophthalmic suspension, USP) 5%, Alcon is an antifungal with wording in the Clinical Pharmacology section that "Systemic absorption should not be expected following topical administration of Natacyn..." This statement is followed by "Studies in rabbits receiving topical natamycin revealed no measurable compound in the aqueous humor or sera..." There are no referenced human studies to support this notion. The reference for this is the PDR for Ophthalmic Medicines, 29th Ed., 2001, page 220.

In these cases, the referenced animal or *in vitro* studies either support an efficacy claim or suggest a safety benefit for the prescriber to consider. Our proposed use of the rabbit studies to explain the once per day dosing of ISTALOL seem to be congruent with the

NDA 21-516

4/5-04 Teleconference

Page 3

foregoing, i.e., the enhanced aqueous humor concentration found in rabbits compared to formulations that do not contain sorbic acid may help explain why once daily dosing of this product in humans is effective.

Based on this rationale, we propose addition of the following to the Clinical Pharmacology section.

[

]

[

]

FDA Response: Rabbit bioavailability does not correlate with human bioavailability. The inclusion of these studies is not recommended.

Original ISTA Question # 4 - Under Adverse Reactions, we believe it is helpful for physicians to know that most of the reported adverse events were mild and that burning and stinging did not cause patients to discontinue use of the drug. These sentences have been deleted. Could these points be retained if they were reworded or appear elsewhere in this section?

Original FDA Response: *No. Disagree that it is well established that no subjects discontinued use of the drug due to burning and stinging.*

This NDA relies, in part, on the FDA's findings of safety and efficacy for timolol maleate ophthalmic solution. These statements are not found in the referenced timolol labeling and imply additional safety over the referenced product.

ISTA Response: We appreciate FDA's comments. However, we believe data specific to this product from the well-controlled study reported in the ISTALOL NDA would be appropriate to include in this product's labeling. The referenced product's labeling states that burning and stinging occur in approximately one in eight patients (12.5%). As currently stated in the ISTALOL labeling, burning and stinging were reported in 38% of patients. To put these findings in perspective for the prescribing physician it is important to note that these events were mostly mild (for 94% of the patients with this AE) and did not cause patients to discontinue treatment. For these reasons, we propose the following

NDA 21-516

4/5-04 Teleconference

Page 4

revised wording (proposed addition in italics): [

1

FDA Response: Burning and stinging was reported more frequently in the Istalol drug product. This is appropriately listed in the proposed labeling. Qualification of these reports is subjective and highly variable. Addition of statements which attempt to minimize the description of adverse events is not recommended.

Additional FDA comments under How Supplied:

a) *Please provide justification of a 2.5 mL fill for this chronic use product.*

ISTA Response: The 2.5 mL fill presentation is to be used as a sample.

FDA Response: Samples should not be listed in the package insert.

b) *In the HOW SUPPLIED section of the package insert, clarify what "No. #####" represents.*

ISTA Response: The NDC product code (No. 003) will be provided here to be used for ordering the product.

FDA Response: Samples should not be listed in the package insert.

c) *Timolol maleate is stated to be a white powder. Please justify the claim of a light yellow solution in the HOW SUPPLIED section of the package insert.*

ISTA Response: The drug substance timolol maleate is a white powder (as stated in the Description section) and the drug product is a clear, colorless to light yellow solution (as stated in the How Supplied section). It is thought that the color comes from potassium sorbate. The drug product description is consistent with the Bausch & Lomb release specification (NDA Amendment 21, Volume 1, page 23). These descriptions of the drug substance and drug product also are consistent with those in the package insert for the referenced product, Timoptic.

FDA Response: Acceptable.

Original ISTA Question # 7 - Clarification of the storage statement.

ISTA Response to FDA Comment: Based on the stability data for the product, the second option will be used, i.e., "Store at 15 °C to 25 °C (59 °F to 77 °F)."

FDA Response: Acceptable.

Carton and Container Labeling

Original ISTA Question #1 - Is the product name as provided on the carton and label acceptable as written?

Original FDA Response: *The prominence and size do not meet CFR 201.10(g)(2).*

ISTA Response: We will revise the labeling to treat "(timolol maleate ophthalmic solution) 0.5%" as the established name.

FDA Response: *Acceptable.*

Original ISTA Question #2 - Some companies provide a timolol equivalent statement as follows: "0.5% Timolol Equivalent (timolol maleate 6.8 mg/mL)". Is this necessary? Or would it be acceptable on the front panel to state "0.5% Timolol Equivalent"?

FDA Response: *Yes, it is necessary.*

FDA Additional comment (a): *For the immediate label, replace "[]" with "6.8 mg timolol maleate equal to 5 mg timolol in each mL". However, there is no requirement for any such statement on the immediate label if it is included on the carton labeling.*

ISTA Question: Please clarify which wording should be used on the carton:

[] or
[] or
6.8 mg timolol maleate equal to 5 mg timolol in each mL

FDA Response: *"6.8 mg timolol maleate equal to 5 mg timolol in each mL" should be used on the carton.*

Original ISTA Question #3 - Is it necessary that the 0.5% Timolol Equivalent statement accompany the product name on each panel, or is it acceptable that this statement appear solely on the major panel?

FDA Response: *It is acceptable for the information on the amount of timolol to appear on only one panel.*

Additional ISTA Questions:

Carton: We understand that the wording to be clarified by Item 2 above only needs to appear on one panel of the carton. Would it be acceptable for this to replace the draft wording: "[]" that now appears on one side panel of the carton?

NDA 21-516

4/5-04 Teleconference

Page 6

Bottle Label: Based on FDA's additional comment (a) quoted above, and because both bottle sizes will be provided in cartons, we propose to delete the [] statement from the bottle labels.

FDA Response: Acceptable.

FDA additional comments on the carton and immediate labels:

b) *If possible, increase the font size for better legibility for the carton and immediate labels.*

ISTA Response: Unfortunately, due to technical limitations of our vendor it is not possible to increase the font size.

FDA Response: Please consider changing when it becomes technically feasible.

c) *Clarify the location of the batch # and expiry date on the carton and immediate labels.*

ISTA Response: The batch # and expiry date will be embossed on the bottom carton panel and will be hot stamped on the bottle label to the left of the "Distributed by" statement.

FDA Response: Acceptable.

d) *Is the carton size the same for both 7.5 mL and 10 mL containers?*

ISTA Response: Yes, it is the same.

FDA Response: Acceptable.

Additional CMC Request:

Please specify the location of [] data for the proposed packaging configurations.

ACTION ITEM:

The Sponsor will provide the specific location of the requested [] data.

Minutes Prepared by: Michael Puglisi
Project Manager

Concurrence by: Wiley A. Chambers, M.D.
Deputy Division Director

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**

Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Marvin Garrett

From: Mike Puglisi, Project Manager

Fax: 949-788-6010

Fax: 301-827-2531

Phone:

Phone: 301-827-2522

Pages: 4 (including cover page)

Date: April 2, 2004

Re: Agency Response to Meeting Questions re: NDA 21-516

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

• **Comments:**

Marv-

Here are our written responses to the two sets of meeting questions, dated March 12 and 19, 2004, concerning labeling for Istalol (NDA 21-516). It is now the policy of the Division to provide written response in advance of Sponsor meetings and teleconferences. Our teleconference is still scheduled for 3:00 pm (Eastern) on Monday, April 5, 2004. Please let me know if you'd like to change those plans or if you have any questions about these comments. Thanks.

-Mike

Ista Pharmaceuticals
Istalol - NDA 21-516
4/5/04 Labeling Telecon

Package Insert Questions/Discussion Points (from 3/12/04 submission):

1. Under Description, we believe there is a typographical error and the pH should be 6.5-7.5.

FDA Response: Agree. pH should read 6.5-7.5.

2. Also under Description, ISTA would like to change [] to "purified water". The manufacturer referenced in the NDA, Bausch & Lomb, uses purified water in the manufacture of ISTALOL.

FDA Response: Agree.

Additional comments on the Description section:

The last two sentences should be in a separate paragraph, i.e., "Each mL of Istalol..." begins the new paragraph.

3. Under Clinical Pharmacology, Pharmacokinetics, we believe the two paragraphs on rabbit studies that have been deleted provide useful information and should remain in the package insert text. Would it be acceptable to keep these paragraphs if we add a new heading for []

FDA Response: No. Disagree that these two paragraphs on animal studies have clinical relevance.

4. Under Adverse Reactions, we believe it is helpful for physicians to know that the most reported adverse events were mild and that burning and stinging did not cause patients to discontinue use of the drug. These sentences have been deleted. Could these points be retained if they were reworded or appear elsewhere in this section?

FDA Response: No. Disagree that it is well established that no subjects discontinued use of the drug due to burning and stinging.

This NDA relies, in part, on the FDA's findings of safety and efficacy for timolol maleate ophthalmic solution. These statements are not found in the referenced timolol labeling and imply additional safety over the referenced product.

5. Also under Adverse Reactions, because headache and hypertension now appear in the introductory paragraph, we propose deleting them below in the Body as a Whole and cardiovascular sections, respectively.

FDA Response: Agree.

6. Under How Supplied, the dropper tip and cap should be 15 mm rather than [1]. Also the 2.5 mL fill is provided in a 7.5 mL bottle rather than a [] bottle.

FDA Response: Agree.

Additional comments:

- a) *Please provide justification of a 2.5 mL fill for this chronic use product.*
 - b) *In the HOW SUPPLIED section of the package insert, Clarify what "No. ####" represents.*
 - c) *Timolol maleate is stated to be a white powder. Please justify the claim of a light yellow solution in the HOW SUPPLIED section of the package insert.*
 - d) *In the HOW SUPPLIED section of the package insert, delete the phrase ' [1]*
7. Clarification of the storage statement.

FDA Response:

The storage statement is "Store at 2 °C to 30 °C (34 °F to 86 °F) provided that 30 °C storage conditions are studied with acceptable results and future annual stability studies will be performed at 30 °C.

The storage statement is "Store at 15 °C to 25 °C (59 °F to 77 °F) if current and future stability studies are carried out at 25 °C.

Ideally, if the range extends to 2°C, refrigerated storage conditions should be included in the current and future stability studies.

Carton and Container Labeling Questions (from 3/19/04 submission):

1. Is the product name, as provided on the carton and label acceptable as written?

FDA Response: The prominence and size does not meet CFR 201.10 (g)(2).

2. Some companies provide a timolol equivalent statement as follows: "0.5% Timolol Equivalent (timolol maleate 6.8 mg/mL)" Is this necessary? Or would it be acceptable on the front panel to state "0.5% Timolol Equivalent"?

FDA Response: Yes, it is necessary.

3. Is it necessary that the 0.5% Timolol Equivalent statement accompany the product name on each panel, or is it acceptable that this statement appear solely on the major panel?

FDA Response: It is acceptable for the information on the amount of timolol to appear on only one panel.

Additional comments on the carton and immediate labels:

- a) For the immediate label, replace ‘ [] with “6.8 mg timolol maleate equal to 5 mg timolol in each mL”. However, there is no requirement for any such statement on the immediate label if it is included on the carton labeling.
- b) If possible, increase the font size for better legibility for the carton and immediate labels.
- c) Clarify the location of the batch # and expiry date on the carton and immediate labels.
- d) Is the carton size the same for both 7.5 mL and 10 mL containers?

Additional General Comments:

- “Rx only” is missing in the package insert
- Further labeling revision may be needed depending on the review of the last major amendment.

**Appears This Way
On Original**

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

/s/

Michael Puglisi
4/2/04 10:26:37 AM



NDA 21-516

3/19/04

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:

We received your March 12, 2004, correspondence on March 15, 2004, requesting a meeting (teleconference) to discuss labeling for Istalol (timolol maleate ophthalmic solution) 0.5%. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You did not indicate the type of meeting requested. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. The meeting is scheduled for April 5, 2004, at 3:00 pm (Eastern Standard Time). Please provide a call-in number at your earliest convenience.

NDA 21-516

Page 2

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
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/

Michael Puglisi
3/19/04 02:51:51 PM
for Carmen DeBellis

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**

Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Marvin Garrett **From:** Mike Puglisi, Project Manager

Fax: 949-788-6010 **Fax:** 301-827-2531

Phone: **Phone:** 301-827-2522

Pages: 2 (including cover page) **Date:** October 28, 2003

Re: Microbiologist's Comments re: NDA 21-516

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● **Comments:**

Marv-

Here are some comments from our Microbiologist concerning NDA 21-516, for Istalol. Please respond in an amendment to your NDA. Let me know if you have any questions about these comments. Thanks.

-Mike

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

1. The [] holding times for the drug product should be established prior to approval by the Agency. A commitment to establish these holding times based upon the completion of process validation batches is not acceptable. Please provide [] holding times for ISTALOL®.
2. The June 5, 2003 response to question 9b states that Senju/ISTA was unable to conduct a container/closure integrity test using components [] because [] had discontinued production of the containers. When a suitable replacement has been found, container/closure integrity testing should be conducted. Be advised that a new container closure system will necessitate another antimicrobial preservative effectiveness test as well. Please submit the results of these tests for review.

**Appears This Way
On Original**

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

/s/

Michael Puglisi
10/28/03 04:50:36 PM

MEETING MINUTES

MEETING DATE: 10/2/03

TIME: 10:30 AM

LOCATION: S400

IND # 59,046

Meeting Request Submission Date - 8/28/00

Date Scheduled - 8/30/00

Meeting Packages Submitted - 9/13/00

DRUG: Timolol Maleate Ophthalmic Solution

SPONSOR: Senju Pharmaceutical Co., Ltd.

TYPE OF MEETING: End of Phase II

FDA PARTICIPANTS:

Wiley Chambers/ Deputy Division Director

Libaniel Rodriguez/Chemist

Bonnie Dunn/Deputy Director, DNDC III

Zhou Chen/Pharmacologist

Jonca Bull/Deputy Director, ODE V

Lucious Lim/Medical Officer

William Boyd/Medical Officer

Stan Lin/Statistics Team Leader

Linda Ng/Chemistry Team Leader

INDUSTRY PARTICIPANTS:

Takahiro Ogawa/Director, Clinical Development

Hideo Terayama/Director, Regulatory Affairs

Noritsugu Inui/Clinical Development Manager

□ □ /Consultant

□ □ /Consultant

Hidemi Shimoji/Director, Clinical Development

Takashi Awata/Director, Planning

Yoshifumi Ikejiri/Regulatory Affairs Manager

QUESTIONS TO THE AGENCY:

1. **Clinical: TIMLA-301:** Is the enclosed double-masked, parallel study in which Timolol LA 0.5% is compared to timolol maleate ophthalmic solution 0.5% adequate to support the efficacy and safety of Timolol LA? We plan to enroll 300 patients (150 per treatment group) to provide 100 patients per treatment group at month 12. Please note that this study includes frequent evaluation of intraocular pressure,

including “peak” and “trough” measurements. This is consistent with the draft guidelines provided to us by FDA at our pre-IND meeting in 1999. However, we did not plan for evaluation of pupil size, endothelial cell count, electrocardiogram or clinical laboratories. Given the long-term experience with timolol, we did not feel that these measures were needed, and that it would not be appropriate to subject subjects to these additional evaluations.

Agency Response: *The proposed primary efficacy endpoint (change from Baseline IOP at the trough assessment time after six (6) months of treatment in the study eye) is unacceptable.*

The primary efficacy variable utilized in the review of the NDA would be the assessment of mean IOP at each specified individual time point (peak and trough). Visit 6 (Month 6) should include dilated ophthalmoscopy. Pupil size, endothelial cell count, electrocardiogram, and clinical lab testing are not needed.

2. **Clinical/Statistical: TIMLA-301:** We planned an interim analysis after all patients have completed 6 months of treatment. We would submit this information in our NDA. When all patients have completed 12 months of treatment, we would submit this information as a safety update. Is six months the optimal time for interim analysis from FDA perspective? Is the statistical section of the protocol appropriate for this type of analysis?

Agency Response: *Agree – an analysis after three or six months completed treatment can be submitted to the NDA. The analysis should be located in the clinical section of the NDA; the clinical and statistical sections should be identical.*

A safety update would be submitted four (4) months after the original submission. 12-month data should be submitted as soon as it is available.

3. **Clinical: Pediatric:** In our pre-IND meeting, we suggested to FDA that a waiver of pediatric requirements might be appropriate, given the nature of open-angle glaucoma as a disease of the aged eye. FDA advised us that as there are children with glaucoma, clinical data would be required. Are pediatric trials still required for this NDA?

Agency Response: *Yes, but may be done as Phase 4 (see Question 5).*

4. **Clinical: Pediatric:** If the answer to the previous question regarding requirement for pediatric data is affirmative, please provide further input on such a study. We reviewed FDA’s classification of age groups as: a) birth to 1 month, b) 1 month to 1 year, c) 1 year to 3 years and d) 3 years to 12 years. Given the relative infrequency of this disorder in children, the logistics of conducting such studies in children, and the fact that by 3 years, the eye is nearly adult in size, we propose

┌
] Does FDA have any comment on this plan, in order to fulfill the pediatric requirements for a subsequent NDA? We considered ┌

]

Agency Response: *The clinical trial outline is not acceptable:*

- *The study should be a randomized, double-masked, parallel comparison trial*
- *At least 30 patients per arm should be evaluated*
- *The study should be of at least 12 weeks duration*
- *The study should include a minimum of four evaluations including baseline and end of treatment.*

The sponsor should obtain a Written Request before submitting a pediatric study to the NDA.

5. **Clinical: Pediatric:** If pediatric data is required, then might this be a Phase 4 commitment, rather than required at time of NDA submission?

Agency Response: *The sponsor would need to formally request a deferral [21 CFR 314.55(b)].*

6. **Clinical: Additional studies:** We are planning a study TIMLA-102 in which the comfort of Timolol LA is compared to Timoptic-XE®. The study design would be similar in nature to our TIMLA-101 (one week, two-period crossover study in normal volunteers). While we may mask the subject, given the different formulations (solution vs. gel forming solution), traditional double-masking may be difficult. Our objective is to provide relative comfort data on Timolol-LA. We assume that FDA would have no issue with such a study.

Agency Response: *Agree, with conditions. Subjects should be instructed not to discuss their medication with others enrolled in the study or in specific detail with the Investigator. The Investigator should not dispense study medication to subjects. A third party in the Investigator's office who is not responsible for patient assessments should be given the responsibility of dispensing study medication to the subject, instilling medication when necessary, and instructing the subject in study medication use.*

Evaluation of comfort should take place after application of the drops. Dosing of the drops should be at least 30 minutes after the use of any anesthetic agent or IOP measurement. To support any claims, studies must be replicated.

7. **Chemistry:** To date we have prepared 2 pilot batches at about ┌] of what we expect to be the commercial batch size of ┌] Will another batch made at least the same volume be sufficient to gain NDA approval?

Agency Response: *With the proposed batches, the NDA can be filed. However, approval will depend on the quality of the data supplied.*

8. **Chemistry:** We have shown that the product is not adversely affected by light (following ICH guidelines) when stored in its primary package. We believe it is not necessary to repeat the photostability evaluation of the drug product with a second source of the API. Do you agree?

Agency Response: *Acceptable. Data should be submitted with the NDA.*

9. **Chemistry:** Senju wishes to provide additional fill volumes for commercialization. Senju wishes to provide 2.5mL, 5mL, 10mL and 15mL for commercialization. Are these fill volumes acceptable by FDA?

Agency Response: *The proposed fill volumes are acceptable. Fill volumes need to be supported by stability data.*

10. **Chemistry:** We intend to utilize a container/closure system for additional fill volume made from the same components as used for our current 10mL bottle. To date we have filled 5mL of the Timolol-LA into the 10mL LDPE (low density polyethylene) bottles. It is our intention to divide the next batch to be manufactured in order to fill both 5mL and additional volumes. These bottles will be placed on the same ACC (accelerated) and LTT (long term testing) stability protocol we are submitting. Given the stability data we have generated along with the significant stability history of the innovator and generic timolol maleate ophthalmic solutions is one batch of product filled with additional volumes and three batches of product filled at 5mL sufficient for NDA approval if the product is shown to be stable after 6 months storage at accelerated and 12 months storage at long term conditions?

Agency Response: *This proposal is acceptable for filing of the NDA, approval will depend on the quality of the data. It is recommended that a minimum of 6 months of accelerated testing stability data be included at the time of NDA submission.*

11. **Chemistry:** We may [] before making a third pilot batch. Given the stability data we have generated (on two pilot batches made at []) along with the significant stability history of the innovator and generic timolol maleate ophthalmic solutions is one batch of product manufactured with additional volumes and one batch filled with 5mL filled [] sufficient for NDA approval if the product is shown to be stable after 6 months storage at accelerated and 12 months storage under long term conditions?

Agency Response: *Yes, see question #10.*

12. **Chemistry:** Alternatively we might [] after making a third pilot batch at [] Given the stability data we have generated along with the significant stability history of the innovator and generic timolol maleate ophthalmic solutions is one batch of product manufactured with additional volumes and one batch filled with 5mL [] sufficient for NDA approval if the product is shown to be stable after 6 months storage at accelerated?

Agency Response: This is a post approval question. Deferred until more information is submitted, possibly at Pre-NDA meeting.

13. **Chemistry:** In [] Given the stability data we have generated along with the significant stability history of the innovator and generic timolol maleate ophthalmic solutions is one batch of product filled with additional volumes and one batch filled with 5mL [] sufficient for NDA approval if the product is shown to be stable after 6 months storage at accelerated?

Agency Response: This is a post-approval question. Deferred until more information is submitted, possibility at Pre-NDA meeting.

14. **Chemistry:** A categorical exemption under 21CFR25.31(b) is requested. Given the long history of use of this product made by the innovator and numerous generic versions will this request be granted?

Agency Response: This proposal is acceptable. Data to support the categorical exclusion should be provided with the NDA.

15. **Chemistry:** May the Phase 3 trials be conducted with more than one lot of product?

Agency Response: Yes, the use of more than one lot of product is acceptable. Information should be included in the NDA.

16. **Regulatory: Timing issues:** May we submit our CMC section of our NDA 30 days prior to the main submission if so desired? Is there any benefit to the Sponsor or to the FDA for such an early submission?

Agency Response: Yes – benefits Sponsor and agency by allowing Reviewers to identify any problems or deficiencies earlier in the review cycle and request inspections.

17. **Regulatory: Clinical data:** May we submit the NDA with 6 month (or 6 month) efficacy data from our TIMLA-301 Phase 3 study?

Agency Response: Yes.

18. **Regulatory: Timing issues:** Given the time required for clinical, preclinical, and chemistry reviews, is there an optimal filing time vis-à-vis a 6 vs. 6 month interim analysis on Study TIMLA-301? That is, given that we plan to file efficacy data at 6 months, and safety update data at 12 months, does that allow for adequate review time?

Agency Response: See response to Question 2.

19. **Regulatory: Exclusivity:** While we understand that the final ruling is made at the time of NDA submission, are we correct in assuming that FDA would provide for 3 years of exclusivity after NDA approval? Would completing the pediatric study TIMLA-302 provide for additional exclusivity?

Agency Response: Theoretically "Yes" to both questions, but final ruling would be made after review of the NDA.

20. **Regulatory: Package insert:** In the clinical pharmacology section of our label, we are considering including information on the results of our study TIMLA-101, and may include information from our study TIMLA-102. This may be information regarding plasma levels or relative comfort. Given our intended 505(b)(2) filing, does FDA have any issue with this plan?

Agency Response: Final labeling decisions will be made after review of the NDA. Labeling of the storage condition should be consistent with the storage conditions in the long term stability studies.

21. **Regulatory:** Please note that we plan to file for only the 0.5% strength of timolol maleate. We would like FDA to confirm that this is acceptable.

Agency Response: Acceptable.

22. **Regulatory:** Do we need to supply any additional information at this time to support a subsequent 505(b)(2) NDA submission?

Agency Response: No. See draft Guidance for Industry regarding 505(b)(2) applications.

23. **Regulatory:** We currently use the name "Timolol LA" to refer to our product. In our pre-IND meeting, FDA commented that this name may be of issue as a brand name. We are in the early stages of trademark searches, and wish further input from FDA at this time. Would FDA consider other names such as []
What about names such as " []

Agency Response: Unlikely that [] " would be acceptable.

Additional Comments: Timolol is typically listed as white or colorless. If there is a change to a yellow color, this should be monitored. If the term 'J' is used, it should be defined.

Prepared by: Michael Puglisi
Project Manager
HFD-550

Concurrence by: Wiley A. Chambers, M.D.
Deputy Division Director
HFD-550

**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
7/23/03 12:23:17 PM

2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

6/24/03

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 12/5/02	DUE DATE: 6/11/03	ODS CONSULT #: 02-0218
-------------------------------	--------------------------	-------------------------------

TO:

Lee Simon
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH:

Mike Puglisi
Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

PRODUCT NAME:

Istalol (Timolol Maleate Ophthalmic Solution)
0.5%

NDA SPONSOR: Senju Pharmaceutical Co., Ltd.

NDA #: 21-516

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Istalol" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, "Istalol".
2. DDMAC finds the proprietary name, "Istalol", acceptable from a promotional perspective.
3. Please submit final product labels and labeling when available.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 6, 2003
NDA NUMBER: 21-516
NAME OF DRUG: Istalol (Timolol Maleate Ophthalmic Solution) 0.5%
NDA HOLDER: Senju Pharmaceutical Co., Ltd.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) for assessment of the tradename "Istalol", regarding potential name confusion with other proprietary and established drug names. The package insert was submitted to the Agency for review. There was no submission of container labels, carton labeling, and patient information sheets.

PRODUCT INFORMATION

"Istalol" is the proposed proprietary name for timolol maleate ophthalmic solution. It is a non-selective beta-adrenergic receptor blocking agent and is indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. "Istalol" will be available in a concentration of 0.5%. The starting dose is one drop in the affected eye once a day.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to "Istalol" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database⁴ and the data provided by Thomson & Thomson's SAEGISTM Online Service⁵ were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov>.

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Istalol". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Panel had look-alike concerns with *Stadol* and sound-alike concerns with *Vistaril* and *Esmolol*. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.
2. DDMAC finds the proprietary name, "Istalol", acceptable from a promotional perspective.

Table 1

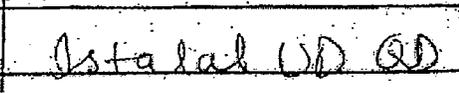
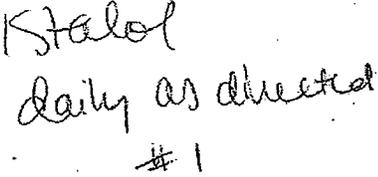
Product Name	Dosage form(s), Generic name	Usual adult dose	Other
Istalol	Etimolol Maleate (Rx) Ophthalmic Solution: 0.5%	One drop into affected eye once a day	
Stadol	Butorphanol Tartrate (Rx) Injection: 1 mg/mL and 2 mg/mL Nasal Spray: 10 mg/mL	Pain <i>IV</i> : 0.5-2 mg repeated every 3 to 4 hours as necessary. <i>IM</i> : 1-4 mg every 3 to 4 hours as necessary. <i>Nasal</i> : 1 mg (1 spray in 1 nostril). If pain relief is not achieved within 60 to 90 minutes, then an additional 1 mg may be given. Preoperative anesthesia: 2 mg IM 60 to 90 minutes before surgery. Balanced anesthesia: 2 mg IV shortly before induction or 0.5 to 1 mg IV in increments during anesthesia. Labor: 1-2 mg IV or IM in patients at full term in early labor; repeat after 4 hours.	LA
Vistaril	Hydroxyzine Pamoate or Hydroxyzine	Anxiety: 50-100 mg 4	SA

Product Name	Dosage form(s), Generic name	Usual adult dose	Other
Istalol	Bimolol Maleate (Rx) Ophthalmic Solution: 0.5%	One drop into affected eye once a day	
	Hydrochloride (Rx) Capsules (Pamoate): 25 mg, 50 mg, and 100 mg Oral Suspension (Pamoate): 25 mg/5 mL Injection (Hydrochloride): 25 mg/mL and 50 mg/mL	times a day. Pruritus: 25 mg 3 or 4 times a day. Sedative: 50 to 100 mg. <u>Antiemetic/Analgesia</u> (adjunctive therapy): 25-100 mg IM as pre- and postoperative/pre- and postpartum adjunctive medication to permit reduction of narcotic dosage.	
Brevibloc	Esmolol Hydrochloride (Rx) Injection: 10 mg/mL and 250 mg/mL	<u>Supraventricular Tachycardia</u> : Initiate treatment with loading dose of 500 mcg/kg/min for 1 minutes followed by a 4-minute maintenance infusion of 50 mcg/kg/min. If no therapeutic effect in 5 minutes, then repeat loading dose and increase maintenance dose to 100 mcg/kg/min. Maintenance dosing range: 50-200 mcg/kg/min.	SA
*Frequently used, not all-inclusive. **SA (sound-alike), LA (look-alike).			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

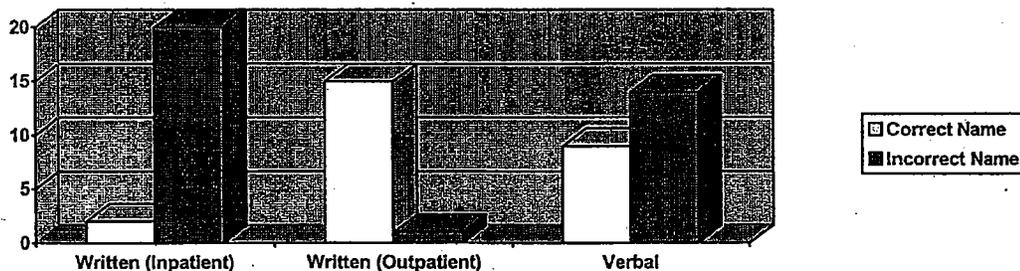
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Istalol" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Istalol" (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Inpatient Rx:</p> 	<p>Outpatient Rx:</p> <p>Istalol. He is to use that daily as directed. Dispense number one please.</p>
<p>Outpatient Rx:</p> 	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Istalol"	Incorrectly Interpreted
Written Inpatient	35	22 (63%)	2 (9%)	20 (91%)
Written Outpatient	32	16 (50%)	15 (94%)	1 (6%)
Verbal Outpatient	39	23 (59%)	9 (39%)	14 (61%)
Total	106	61 (58%)	26 (43%)	35 (57%)



Among the written inpatient prescriptions, 20 out of 22 respondents (91%) interpreted "Istalol" incorrectly. Misinterpretations included *Istalal* (15 respondents, 68%), *Istabal* (1 respondent, 5%), *Istalad* (1 respondent, 5%), *Istalub* (1 respondent, 5%), *Sotalol* (1 respondent, 5%), and *Istatab* (1 respondent, 5%). One respondent interpreted "Istalol" as *Sotalol*, which is an existing drug product on the U.S. market.

Among the written outpatient prescriptions, 1 out of 16 respondents (6%) interpreted "Istalol" incorrectly. The respondent misinterpreted "Istalol" as *Stalol*. None of the respondents interpreted "Istalol" as an existing U.S. marketed drug product.

Among the verbal outpatient prescriptions, 14 out of 23 respondents (61%) interpreted "Istalol" incorrectly. Misinterpretations included *Histalol* (2 respondents, 9%), *Istolol* (2 respondents,

9%), *Isterol* (1 respondent, 5%), *Isthokol* (1 respondent, 5%), *Isthalol* (1 respondent, 5%), *Hismalol* (1 respondent, 5%), *Istidol* (1 respondent, 5%), *Istilol* (1 respondent, 5%), *Isteral* (1 respondent, 5%), *Istelol* (1 respondent, 5%), *Istorol* (1 respondent, 5%), and *Histolol* (1 respondent, 5%). *Hismalol* is very similar to *Hismanal*; however, *Hismanal* was voluntarily discontinued by Janssen Pharmaceutica in 1999. None of the respondents interpreted "Istalol" as an existing U.S. marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Istalol", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names include *Stadol*, *Vistaril*, *Esmolol*, and *Sotalol*.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that "Istalol" can be confused with *Sotalol*. One study participant misinterpreted "Istalol" as *Sotalol* on a written order. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The remaining interpretations from the verbal and written prescription studies were phonetic/misspelled variations of the drug name "Istalol".

Stadol looks similar to "Istalol". *Stadol* contains butorphanol tartrate and is indicated for the management of pain (including postoperative analgesia), preoperative or presanesthetic medication, relief of pain during labor, and to supplement balanced anesthesia. The nasal spray has been shown in clinical trials to be effective in the treatment of migraine headache pain. Even though *Stadol* and "Istalol" overlap in the "sta" and "ol" letters and the "d" in *Stadol* can be scripted to look like an "l", the "I" in "Istalol" may differentiate the two names from each other. However, if the "I" is written very small or is scripted in a certain way, "Istalol" can look similar to *Stadol* (see page 7). Both drug products are in liquid form; however, they differ in dosage form (injection and nasal spray vs. ophthalmic drops), route of administration (parenteral and nasal vs. eye), strength (1 mg/mL, 2 mg/mL, and 10 mg/mL vs. 0.5 %), and directions of use (every three to four hours, before surgery/labor, or when in pain (nasal) vs. once a day). There may be less of a confusion between these two products in an inpatient pharmacy setting since there are three strengths of *Stadol* and one strength of "Istalol". However, in a community pharmacy where *Stadol* is usually dispensed in the nasal spray form, a pharmacist may receive a prescription for "Stadol, use as directed, #1," but he or she may interpret the prescription as "Istalol, use as directed, #1." If *Stadol* was accidentally dispensed instead of "Istalol", then the patient's ocular hypertension or glaucoma would not be adequately treated. If the patient's condition is left untreated for a certain period of time, the patient may become blind. Also, a patient may spray the *Stadol* in his or her eyes, which may cause injury to the eye(s) such as irritation and pain. If the patient mistakenly received "Istalol" instead of *Stadol*, then the patient's pain would not be adequately controlled. If there is any systemic absorption through the nasal site, then the patient may experience cardiac effects as well as severe respiratory reactions in patients with asthma. The similarities between "Istalol" and *Stadol* may increase the potential risk of medication error occurrences between these two drug products, which may result in patients experiencing unnecessary side effects.

Written Sample:

Istalol

Stadol

Istalol

Stadol

Esmolol sounds similar to "Istalol". *Esmolol hydrochloride* is the established name for *Brevibloc*. It is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in preoperative, postoperative, or other emergent circumstances where short-term control of ventricular rate with a short-acting agent is desirable. It is also indicated when a rapid heart rate requires specific intervention, and is also for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period. The "es" in *esmolol* sounds similar to "is" in "Istalol" as well as the "olol" and "alol". Four respondents from the verbal portion of the study interpreted "Istalol" with an "olol" ending. Even though *esmolol* is actually "esmolol hydrochloride", a practitioner may just prescribe "esmolol". The "hydrochloride" does not distinguish the two names from each other. These two drug products are available as a solution, but they differ in dosage form (injection vs. ophthalmic drops), strength as well as the number of strengths (10 mg/mL and 250 mg/mL vs. 0.5%), route of administration (parenteral vs. ophthalmic), and the directions of use (loading dose of 500 mcg/kg/min for one minute followed by a maintenance dose of 50 mcg/kg/min vs. one drop into affected eye once a day). These differences may prevent the wrong drug from being administered to the patient; however, since *esmolol* and "Istalol" sound very similar, it may not prevent the dispensing of the wrong drug. If "Istalol" was dispensed instead of *esmolol* in an emergency situation, the delay of the administration of *esmolol* may have serious consequences in a patient experiencing supraventricular tachycardia, noncompensatory sinus tachycardia, or intraoperative and postoperative tachycardia and hypertension. Also, "Istalol", a beta blocker, can be absorbed systemically. If "Istalol" was administered to a patient with cardiac problems, the administration of "Istalol" may aggravate the patient's problems. If *esmolol* was accidentally administered, the patient may experience cardiac adverse events as well as not receive his/her glaucoma or ocular hypertension treatment. The similarities between "Istalol" and *esmolol* may increase the potential risk of medication error occurrences between these two drug products, which may result in patients experiencing unnecessary side effects.

Sotalol was also identified as a potential look-alike name. In the written portion of the study, one respondent interpreted "Istalol" as *sotalol*. *Sotalol* (a beta-adrenergic blocking agent) is the established name for *Betapace* and *Betapace AF*. *Betapace* is indicated for ventricular arrhythmias and the initial recommended dose is 80 mg twice a day. The dose may then be increased, if necessary, to 120 - 160 mg twice a day. *Betapace AF* is indicated for the maintenance of normal sinus rhythm in patients with symptomatic AFIB/AFL who are currently

in sinus rhythm. The dose for *Betapace AF* is individualized according to a patient's creatinine clearance. The recommended initial dose is 80 mg and can be titrated up to 120 mg. *Betapace AF* can be administered once a day to twice a day. *Betapace* and *Betapace AF* are available as a 80 mg, 120 mg, 160 mg, and 240 mg tablet. *Betapace* is also available as a 240 mg tablet. Both names, sotalol and "Istalol", look similar when scripted (see below). Even though *sotalol* is actually "sotalol hydrochloride", a practitioner may just prescribe "sotalol". The "hydrochloride" does not distinguish the two names from each other. *Sotalol (Betapace AF)* and "Istalol" can be given once a day. However, they differ in dosage form (tablets vs. ophthalmic drops), route of administration (oral vs. ophthalmic), and strength as well as the number of strengths (80 mg, 120 mg, 160 mg, and 240 mg vs. 0.5%). These differences may prevent the wrong drug from being administered to the patient; however, since *sotalol* and "Istalol" look very similar, they may not prevent the dispensing of the wrong drug. If "Istalol" was dispensed instead of *sotalol* in an emergency situation, the delay of the administration of *sotalol* may have serious consequences in a patient experiencing serious ventricular arrhythmias. "Istalol", a beta blocker, can be absorbed systemically. If "Istalol" was administered to a patient with cardiac problems, the administration of "Istalol" may aggravate the patient's problems. If *sotalol* was accidentally administered, the patient may experience cardiac adverse events as well as not receive his/her glaucoma or ocular hypertension treatment. Given that "Istalol" and *sotalol* can look similar, as evidenced by the interpretation of one respondent from the study, these two drug products have a potential of being confused with each other. A patient may experience unnecessary serious side effects if they were administered the wrong medication. The similarities between "Istalol" and *sotalol* may increase the potential risk of medication error occurrences between these two drug products, which may result in patients experiencing unnecessary side effects.

Writing Sample:

Sotalol

Istalol

Vistaril sounds similar to "Istalol". *Vistaril* contains hydroxyzine pamoate or hydroxyzine hydrochloride and is indicated for the symptomatic relief of anxiety that is manifested from a variety of conditions. It is also indicated for the management of pruritus caused by allergic conditions such as chronic urticaria, atopic and contact dermatoses, and in histamine-mediated pruritis. The oral product can be used as a sedative when used as premedication and following general anesthesia. The injection form can be used to control nausea and vomiting (not from pregnancy) as well as a pre- and postoperative and pre- and postpartum adjunctive medication to control emesis and to reduce narcotic dosage. The "vist" in *Vistaril* and the "ist" in "Istalol" sounds similar. The "v" sound in *Vistaril* can be missed sometimes when the name is communicated verbally. The "aril" in *Vistaril* and "alol" in "Istalol" may sound similar; however, the pronunciation of the "r" in "aril" as well as the "ol" makes it sound different from "alol". These two drug products differ in dosage form (capsule, syrup, oral suspension, and injection vs. ophthalmic drops), strength (25 mg, 50 mg, 100 mg, 25 mg/5 mL, 25 mg/mL, and 50 mg/mL vs. 0.5%), route of administration (oral and parenteral vs. ophthalmic), and directions of use (three to four times a day or before procedure or event vs. once a day). These differences

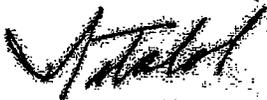
would decrease the potential risk of a medication error occurring between these two drug products.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name Istalol. Istalol has the potential to sound and/or look-like the currently marketed products, Stadol, Esmolol, and Sotalol.

Stadol looks similar to "Istalol". *Stadol* contains butorphanol tartrate and is indicated for the management of pain (including postoperative analgesia), preoperative or presanesthetic medication, relief of pain during labor, and to supplement balanced anesthesia. The nasal spray has been shown in clinical trials to be effective in the treatment of migraine headache pain. Even though *Stadol* and "Istalol" overlap in the "sta" and "ol" letters and the "d" in *Stadol* can be scripted to look like an "I", the "I" in "Istalol" may differentiate the two names from each other. However, if the "I" is written very small or is scripted in a certain way, "Istalol" can look similar to *Stadol* (see below). Both drug products are in liquid form; however, they differ in dosage form (injection and nasal spray vs. ophthalmic drops), route of administration (parenteral and nasal vs. eye), strength (1 mg/mL, 2 mg/mL, and 10 mg/mL vs. 0.5 %), and directions of use (every three to four hours, before surgery/labor, or when in pain (nasal) vs. once a day). There may be less of a confusion between these two products in an inpatient pharmacy setting since there are three strengths of *Stadol* and one strength of "Istalol". However, in a community pharmacy where *Stadol* is usually dispensed in the nasal spray form, a pharmacist may receive a prescription for "Stadol, use as directed, #1," but he or she may interpret the prescription as "Istalol, use as directed, #1." If *Stadol* was accidentally dispensed instead of "Istalol", then the patient's ocular hypertension or glaucoma would not be adequately treated. If the patient's condition is left untreated for a certain period of time, the patient may become blind. Also, a patient may spray the *Stadol* in his or her eyes, which may cause injury to the eye(s) such as irritation and pain. If the patient mistakenly received "Istalol" instead of *Stadol*, then the patient's pain would not be adequately controlled. If there is any systemic absorption through the nasal site, then the patient may experience cardiac effects as well as severe respiratory reactions in patients with asthma. The similarities between "Istalol" and *Stadol* may increase the potential risk of medication error occurrences between these two drug products, which may result in patients experiencing unnecessary side effects.

Written Sample:



Istalol



Stadol



Istalol



Stadol

Esmolol sounds similar to "Istalol". *Esmolol hydrochloride* is the established name for *Brevibloc*. It is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter

in peroperative, postoperative, or other emergent circumstances where short-term control of ventricular rate with a short-acting agent is desirable. It is also indicated when a rapid heart rate requires specific intervention, and is also for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period. The "es" in *esmolol* sounds similar to "is" in "Istalol" as well as the "olol" and "alol". Four respondents from the verbal portion of the study interpreted "Istalol" with an "olol" ending. Even though *esmolol* is actually "esmolol hydrochloride", a practitioner may just prescribe "esmolol". The "hydrochloride" does not distinguish the two names from each other. These two drug products are available as a solution, but they differ in dosage form (injection vs. ophthalmic drops), strength as well as the number of strengths (10 mg/mL and 250 mg/mL vs. 0.5%), route of administration (parenteral vs. ophthalmic), and the directions of use (loading dose of 500 mcg/kg/min for one minute followed by a maintenance dose of 50 mcg/kg/min vs. one drop into affected eye once a day). These differences may prevent the wrong drug from being administered to the patient; however, since *esmolol* and "Istalol" sound very similar, it may not prevent the dispensing of the wrong drug. If "Istalol" was dispensed instead of *esmolol* in an emergency situation, the delay of the administration of *esmolol* may have serious consequences in a patient experiencing supraventricular tachycardia, noncompensatory sinus tachycardia, or intraoperative and postoperative tachycardia and hypertension. Also, "Istalol", a beta blocker, can be absorbed systemically. If "Istalol" was administered to a patient with cardiac problems, the administration of "Istalol" may aggravate the patient's problems. If *esmolol* was accidentally administered, the patient may experience cardiac adverse events as well as not receive his/her glaucoma or ocular hypertension treatment. The similarities between "Istalol" and *esmolol* may increase the potential risk of medication error occurrences between these two drug products, which may result in patients experiencing unnecessary side effects.

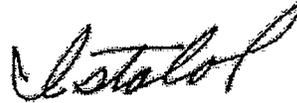
Sotalol was also identified as a potential look-alike name. In the written portion of the study, one respondent interpreted "Istalol" as *sotalol*. *Sotalol* (a beta-adrenergic blocking agent) is the established name for *Betapace* and *Betapace AF*. *Betapace* is indicated for ventricular arrhythmias and the initial recommended dose is 80 mg twice a day. The dose may then be increased, if necessary, to 120 - 160 mg twice a day. *Betapace AF* is indicated for the maintenance of normal sinus rhythm in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. The dose for *Betapace AF* is individualized according to a patient's creatinine clearance. The recommended initial dose is 80 mg and can be titrated up to 120 mg. *Betapace AF* can be administered once a day to twice a day. *Betapace* and *Betapace AF* are available as a 80 mg, 120 mg, 160 mg, and 240 mg tablet. *Betapace* is also available as a 240 mg tablet. Both names, sotalol and "Istalol", look similar when scripted (see page 11). Even though *sotalol* is actually "sotalol hydrochloride", a practitioner may just prescribe "sotalol". The "hydrochloride" does not distinguish the two names from each other. *Sotalol (Betapace AF)* and "Istalol" can be given once a day. However, they differ in dosage form (tablets vs. ophthalmic drops), route of administration (oral vs. ophthalmic), and strength as well as the number of strengths (80 mg, 120 mg, 160 mg, and 240 mg vs. 0.5%). These differences may prevent the wrong drug from being administered to the patient; however, since *sotalol* and "Istalol" look very similar, they may not prevent the dispensing of the wrong drug. If "Istalol" was dispensed instead of *sotalol* in an emergency situation, the delay of the administration of *sotalol* may have serious consequences in a patient experiencing serious ventricular arrhythmias. "Istalol", a beta blocker, can be absorbed systemically. If "Istalol" was administered to a patient with cardiac problems, the administration of "Istalol" may aggravate the patient's problems. If *sotalol* was accidentally administered, the patient may experience cardiac adverse events as well as not receive his/her glaucoma or ocular hypertension treatment. Given that "Istalol" and *sotalol* can look similar, as evidenced by the interpretation of one respondent from the study, these two drug products have a potential of being confused with each other. A patient may experience unnecessary serious side effects if they were administered the wrong medication. The similarities between "Istalol" and *sotalol*

may increase the potential risk of medication error occurrences between these two drug products, which may result in patients experiencing unnecessary side effects.

Writing Sample:



Sotalol



Istalol

IV. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name "Istalol".
2. DDMAC finds the proprietary name, "Istalol", acceptable from a promotional perspective.
3. Please submit final product labels and labeling when available.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
6/24/03 03:29:46 PM
PHARMACIST
Entered into DFS for Jennifer Fan

Carol Holquist
6/24/03 03:54:12 PM
PHARMACIST

Jerry Phillips
6/24/03 08:39:41 PM
DIRECTOR

4 Page(s) Withheld



 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Brandon Wool, M.D.
315 Metairie Road, Suite 302
Metairie, Louisiana 70005

MAY 8 2003

Dear Dr. Wool:

On February 4-5, 2003, Ms. Traci Armand and Ms. Daphne Videau, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # TIMLA-301-PC-1 entitled: "A double-masked, randomized, parallel study of the safety and efficacy of Timolol-LA in patients with ocular hypertension or open-angle glaucoma") of the investigational drug timolol, performed for Senju Pharmaceutical Co. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that, except for a minor issue with study drug accountability records, you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigators Armand and Videau during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me, by letter, at the address given below.

Sincerely,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI:

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why: The issue with the study drug accountability was valid and significant.

Deficiencies noted:

inadequate drug accountability (04)

Deficiency Codes: 4

cc:

HFA-224

HFD-550 Doc.Rm. NDA# 21-516

HFD-550 Review Div.Dir. Simon

HFD-550 Review Dep Div.Dir. Chambers

HFD-550 MO Boyd

HFD-550 PM Puglisi

HFD-47c/r/s/ GCP File # 10881

HFD-47 GCP Shibuya/Storms

HFR-SE-450 DIB Debo

HFR-SE-450 Bimo Monitor Roosevelt

HFR-SE-450 Field Investigator Armand

GCF-1 Seth Ray

r/d: (RS/5/5/03):

reviewed:AEH:5/6/03

f/t.ml:5/7/03

o:\RS\NDA21-516\Wool.doc

Reviewer Note to Rev. Div. M.O.

- This site consented 32 subjects, randomized 28, dropped 5, and completed 23.
- All subjects consented to the study.
- One discrepancy in study drug accountability was documented.
- Data appear acceptable.

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

/s/

Antoine El-Hage
5/12/03 12:07:07 PM

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Marvin J. Garrett

From: Mike Puglisi

Fax: 949-727-0833

Fax: 301-827-2531

Phone:

Phone: 301-827-2522

Pages: 2 (incl. cover)

Date: March 28, 2003

Re: Extractables Testing - NDA 21-516

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● **Comments:**

Marv-

As a follow up to our telecon on Tuesday, the Chemists have provided the attached proposal for extractables testing; Please let me know if you have any questions about this matter. Thanks.

-Mike

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Puglisi
Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 24

James Hart, M.D.
Hart Ophthalmology Associates, PSC
300.South 8th Street, Suite 284 W
Murray, Kentucky 42071

Dear Dr. Hart:

On February 4-6, 2003, Mr. Robert Hudson, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # TIMLA-301-PC-1 entitled: "A double-masked, randomized, parallel study of the safety and efficacy of Timolol-LA in patients with ocular hypertension or open-angle glaucoma") of the investigational drug timolol-LA, performed for Senju Pharmaceutical. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Hudson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI:

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

cc:

HFA-224
HFD-550 Doc.Rm. NDA#21-516
HFD-550 Simon
HFD-550 Boyd
HFD-550 Puglisi
HFD-47c/r/s/ GCP File #10834
HFD-47 Shibuya
HFD-47 Storms
HFR-CE-450 DIB Heppe
HFR-CE-450 Bimo Monitor Eastham
HFR-CE-4550 Field Investigator Hudson
GCF-1 Seth Ray

r/d: (RS3/11/03):

reviewed:AEH:3/12/03

f/t:ml:3/13/03

o:\RS\NDA 21-516\Hart.doc

Reviewer Note to Rev. Div. M.O.

- This site screened 101 subjects, consented 34, randomized 21, dropped 2, and completed 19.
- Records for 8 of the 19 completed subjects were inspected in detail.
- All subjects consented to the trial.
- No regulatory violations were documented.
- Data appear acceptable.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rugieri

Food and Drug Administration
Rockville MD 20857

MAR 24 2003

Walter G. Atlas, M.D.
Charlotte Eye, Ear, Nose & Throat Associates, PS
6035 Fairview Road
Charlotte, North Carolina 28210

Dear Dr. Atlas:

Between January 13-15, 2003, Ms. Eileen Bannerman, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # TIMLA-301-PC-1 entitled: "A double-masked, randomized, parallel study of the safety and efficacy of Timolol-LA in patients with ocular hypertension or open-angle glaucoma") of the investigational drug timolol maleate, performed for Senju Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Bannerman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Walter G. Atlas, M.D.

FEI:

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

cc:

HFA-224

HFD-550 Doc.Rm. NDA# 21516

HFD-550 Review Div.Dir.

HFD-550 MO (Boyd)

HFD-550 PM (Puglisi)

HFD-46/47c/r/s/ GCP File # 10844

HFD-47 Shibuya/Storms

HFR-SE150 DIB (Todd-Murrell)

HFR-SE150 Bimo Monitor (Hubbard)

HFR-SE150 Field Investigator (Bannerman)

GCF-1 Seth Ray

r/d:Storms:3/19/03

reviewed:AEH:3/20/03

f/t:ml:3/20/03

o:\KMS\atlasltr

Reviewer Note to Rev. Div. M.O.

- This site enrolled 19 subjects with all subjects receiving treatment in both eyes; 4 subjects dropped out due to adverse events.
- All serious adverse events were adequately reported (one subject had two total knee arthroplastys; other SAEs reported included hip replacement, transient vision loss, skin cancer, basal cell carcinoma, and microdiskectomy).
- A total of seven subjects' files were reviewed to verify source document information (enrollment forms, consent forms, adverse events, drug accountability records and test results) with the case report forms.
- All subjects received adequate consent.
- Data appear acceptable.

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**

Center for Drug Evaluation and Research, HFD-550

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Marvin J. Garrett

From: Mike Puglisi

Fax: 949-727-0833

Fax: 301-827-2531

Phone:

Phone: 301-827-2522

Pages: 3 (incl. cover)

Date: March 5, 2003

Re: Microbiology Information Request for NDA 21-516

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● **Comments:**

Marv-

Here are the comments/deficiencies that the Microbiology reviewer has noted during his review of NDA 21-516 for timolol maleate ophthalmic solution. Please respond in an amendment to the NDA. Please let me know if you have any questions about these comments. Thanks.

-Mike

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

1. Provide the [redacted] [redacted] the critical manufacturing area.
2. Provide the [redacted] [redacted] limits for the [redacted] [redacted].
3. Even though the product contains a preservative, the [redacted] [redacted] holding times and the [redacted] [redacted] limit should be provided. Actions taken when this limit is exceeded should also be provided.
4. Provide [redacted] [redacted] cycles listed on p. 16 (volume 5).
5. With regard to [redacted] [redacted] equipment:
 - a) Describe how the validation runs conducted [redacted] [redacted]. Please note that [redacted] [redacted] validations should be conducted.
 - b) Provide the manufacturer, [redacted] [redacted].
 - c) Indicate the differences [redacted] [redacted].
6. Regarding [redacted] [redacted] for the container/closure system:
 - a) Will any [redacted] [redacted] other than the two described in attachment I be used for [redacted] [redacted]. If so, please provide a summary of the number and types of components [redacted] [redacted].
 - b) Provide the frequency with which the component bioburden is checked [redacted] [redacted].
 - c) Provide a letter of authorization for DMF [redacted] [redacted] and specify which volume(s) and pages of the DMF are pertinent to NDA 21-516.
7. Regarding media fills:
 - a) Provide the results of environmental monitoring conducted during the three media fills summarized in attachment J.

b) The media should be tested to insure its ability to support microbial growth. Please provide the media control data for these three media fills.

c) On p. 19 of volume 5, it says that all of the media filled [] of batch # 11111 (volume 5, p. 112) says that although [] [] were filled, only [] were [] However, the summary [] Please explain.

8. Please provide the frequency and locations of WFI sampling.

9. Regarding the container/closure integrity test:

a) How much [] []

b) Integrity testing should be conducted with container components. [] []

10 A [] container/closure integrity test should be conducted as part of the stability protocol.

**Appears This Way
On Original**

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Gary D. Novack, Ph.D.

From: Mike Puglisi

Fax: 415-472-2183

Fax: 301-827-2531

Phone:

Phone: 301-827-2522

Pages: 1 (incl. cover)

Date: January 14, 2003

Re: CMC Information Request for NDA 21-516

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.
Thank you.

● **Comments:**

Gary-

Dr. Khorshidi has asked me to convey the following CMC information request concerning NDA 21-516:

Please provide the results of the analysis **at release** for the registration batches of the drug products.

Please let me know if you have any questions about this request. Thanks.

-Mike

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-516	Efficacy Supplement Type	Supplement Number
Drug: Istalol (timolol maleate ophthalmic solution) 0.5%		Applicant: Senju Pharmaceutical Co., Ltd.
RPM: Michael Puglisi		HFD- 550 Phone # 72522
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 18-086, Timoptic
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		Type 3
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		6/16/04
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None
		Subpart H
		<input type="checkbox"/> 21 CFR 314.510 (accelerated approval)
		<input type="checkbox"/> 21 CFR 314.520 (restricted distribution)
		<input type="checkbox"/> Fast Track
		<input type="checkbox"/> Rolling Review
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business
		<input type="checkbox"/> Public health
		<input type="checkbox"/> Barrier-to-Innovation
		<input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation
		<input type="checkbox"/> No-fee 505(b)(2)
		<input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input checked="" type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV
		21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		
		X

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE – 7/25/03
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	Package insert – 5/11/04
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	ODS/DMETS – 10/3/03, 5/14/04 DDMAC – 10/7/03 Labeling Meeting – 4/5/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	5/6/04
• Reviews	ODS/DMETS – 10/3/03, 5/14/04 DDMAC – 10/7/03 Labeling Meeting – 4/5/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	10/2/03
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
❖ Clinical review(s) (indicate date for each review)	7/17/03, 6/4/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	In 7/17/043, Clinical Review
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	6/3/03
❖ Biopharmaceutical review(s) (indicate date for each review)	3/11/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	7/8/03, 5/24/04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	7/8/03
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	3/4/03, 10/17/03, 5/12/04
❖ Facilities inspection (provide EER report)	Date completed: 5/10/04 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	12/13/02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

MEMORANDUM OF TELECON

DATE: December 3, 2002

APPLICATION NUMBER: NDA 21-516

BETWEEN:

Name: Gary D. Novack, Ph.D.
U.S. Representative
Phone: 415-472-2181
Representing: Senju Pharmaceutical Co., Inc.

AND

Name: H. Shawn Khorshidi/ Review Chemist
and Michael Puglisi/ Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550

SUBJECT: CMC Information Request for the original NDA 21-516

Dr. Khorshidi requested that the following information be submitted to the NDA:

1. Information concerning Reference Standards for the drug substance (DS) and drug product (DP), including the lot numbers of the DS and DP that were used as the Reference Standards.
2. Information that shows the link between batches of DS and DP. (i.e. which batches of DS were used to manufacture which batches of DP?)
3. An explanation of the reasons for differences in in-house testing for the DS []
[] There appear to be differences in the tests and limits/specifications.
4. An explanation of the reasons for differences between [] in-house specification for DS and the Drug Master File specification.

Dr. Novack agreed to gather the information and submit it to the NDA as soon as possible.

Prepared By: Michael Puglisi
Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550



NDA 21-516

10/1/02

Senju Pharmaceutical Co., Ltd.
c/o PharmaLogic Development
Attention: Gary D. Novack, Ph.D.
President
17 Bridgegate Drive
San Rafael, CA 94903-1093

Dear Dr. Novack:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Timolol Maleate Ophthalmic Solution

Review Priority Classification: Standard (S)

Date of Application: September 25, 2002

Date of Receipt: September 26, 2002

Our Reference Number: NDA 21-516

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 25, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 26, 2003.

We acknowledge that pediatric studies for your application have been deferred, as stated in our August 27, 2002, letter.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do

not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
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/

Michael Puglisi
10/1/02 10:45:46 AM
for Carmen DeBellas