

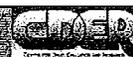
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-516**

**Chemistry Review(s)**

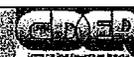


**NDA 21-516**

**ISTALOL<sup>®</sup>**  
**(timolol maleate ophthalmic solution, 0.5%)**

**Senju Pharmaceutical Co., Ltd**

**Hossein S. Khorshidi**  
**Division of Anti-Inflammatory/Analgesics & Ophthalmic**  
**Drug Products**  
**HFD-550**



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# Chemistry Review Data Sheet

1. NDA # 21-516

2. REVIEW # 2

3. REVIEW DATE: 5/14/04

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

<u>Submission</u>	<u>Date</u>
Original	9/25/02
Amendment	12/17/02
Amendment	1/23/03
Amendment	1/9/03
Amendment	2/14/03
Amendment	4/23/04

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission</u>	<u>Date</u>
Amendment	5/30/03
Amendment	6/5/03
<b>Amendment AC</b>	<b>12/6/03</b>
Amendment	12/15/03
Amendment	3/18/04
Amendment	4/22/04
Amendment	5/4/04
Amendment	5/5/04
Amendment	5/11/04

7. NAME & ADDRESS OF APPLICANT:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Name: Senju Pharmaceutical Co., Ltd  
c/o ISTA Pharmaceuticals, Inc.

Address: 15279 Alton Parkway,  
Suite 100, Irvine CA 92618

Representative: Marvin Garrett, Vice president, Regulatory Affairs

Telephone: (949) 788-5303

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Istalol<sup>®</sup> (timolol maleate ophthalmic solution), 0.5%
- b) Non-Proprietary Name (USAN): Timolol Maleate USP
- c) Code Name/# (138):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of ocular hypertension or open angle glaucoma.

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed



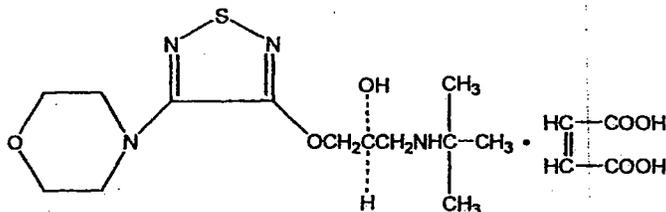
# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

X  Not a SPOTS product

### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$   
Molecular Wt. 432.49

2-Propanol, [(1,1-dimethylethyl)amino]-3-[(4-(4-morpholinyl)-1,2,5-thiadiazole-3-yl)oxy]-, (S)-, (Z)-2-butenedioate(1:1) (salt)

#### Other chemical name:

(-)-1(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazole-3-yl)oxy]-2-propanol maleate (1:1) (salt).

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	II			3	Adequate	6/25/02	
1	II			1	Adequate	12/15/02	
1	III			3	Adequate	3/27/02	
1	III			3	Adequate	10/22/03	



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

9197	III	[ ]	3	Adequate	10/8/93	
12767	III	[ ]	1	Adequate	5/5/04	
4251	III	[ ]	3	Adequate	8/31/98	
3375	III	[ ]	1	Adequate	1/24/03	
			1	Adequate	2/6/04	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-086	Timoptic®(timolol maleate) Solution
ANDA	74-466	Timolol Maleate Ophthalmic solution, 0.5% USP
ANDA	74-516	Timolol Maleate Ophthalmic solution, 0.5% USP

18. STATUS:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable		H. Khorshidi, Ph.D.
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	To be sent (refer to section V of this review)		
OPDRA			
EA	Acceptable	5/14/04	H. Khorshidi, Ph.D.
Microbiology	Acceptable	4/27/04	S.E. Langille, Ph.D.

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On Original*



# The Chemistry Review for NDA # 21-516

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommended for Approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(2). Senju Pharmaceutical has not performed an extensive clinical trials for this product. The company has relied on the Agency's previous finding of safety and efficacy for the listed drugs as well as published clinical studies performed with similar marketed products, for exp., Timoptic® (NDA 18-086) solution and other generic brands including; ANDAs 74-466 and 74-516, Timolol Maleate Ophthalmic Solution. The proposed product is covered by U.S. patent No. 6,335,335

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Two suppliers; [redacted] DMF # [redacted] and [redacted] (DMF # [redacted]) were initially identified as manufacturers of Timolol Maleate, USP (CAS No. 26921-17-5). According to the applicant, [redacted] was considered as the primary source and the [redacted] as a secondary supplier. On May 6<sup>th</sup>, 2004, the applicant has withdrawn [redacted] as supplier of the drug substance for this product. All issues pertaining to the drug substance were resolved in review #1, and therefore, is acceptable.

Drug product:

The original NDA submitted on September 25, 2002 identified [redacted] as the contract manufacturing facility for the drug product. Due to unresolved cGMP compliance issues with [redacted] manufacturing facility, the applicant (Senju/ISTA) has identified "Bausch & Lomb" as an alternative contract manufacturing facility for the finished drug product.



## CHEMISTRY REVIEW



### Executive Summary Section

Manufacturing process consists of [redacted]

[redacted] In general, the drug product manufacturing process in Bausch & Lomb is similar to [redacted] process with a few exceptions such as; [redacted]

[redacted]. These changes are minor and will not affect the overall quality of the drug product. As far as the in-process controls are concerned, both the bulk solution and the filled product are tested. The tests such as pH, osmolality, bioburden, [redacted] fill volume and [redacted] are among the important in-process testing and controls.

Adequate drug product tests and specification is provided. The critical tests include; assay, impurities, potassium sorbate assay, osmolality, pH, benzalkonium chloride assay, and sterility.

The supplier of the container/closure has changed from [redacted]

[redacted] due to discontinuation of supply of the packaging components by [redacted]. This change did not show to have an impact on the quality of the packaging systems [redacted] are the same. In Bausch & Lomb, the final product are filled into two packaging configurations; 2.5 ml fill in 7.5 cc LDPE bottle (physician sample) and 5 ml fill in 10 cc LDPE bottle (commercial sample). Comparing to [redacted] packaging system, in Bausch & Lomb, the 7.5 ml bottle has replaced the [redacted] bottle and also the method of sterilization of the packaging components has been changed [redacted].

The applicant has submitted three months of the stability data (accelerated condition) from three registration batches from Bausch & Lomb ([redacted] batch size). In addition, up to [redacted] months of the long term data and [redacted] months of accelerated stability data from several [redacted] batches (as supportive stability data) are also submitted. Adequate stability protocols and test parameters are provided. The submitted stability data support the proposed expiration dating period of 24 months for this product.

The inspection results for all requested sites have been acceptable by the Office of Compliance.

#### **B. Description of How the Drug Product is Intended to be Used**

Istalol® (timolol maleate ophthalmic solution, 0.5%) is a preserved, multi-dose solution of timolol maleate containing potassium sorbate. The drug is used topically.

Recommended dose is one drop in the affected eye(s) once a day. According to the package insert, if the patient's intraocular pressure is not a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. Based on provided stability data, the applicant has proposed 24 months of expiry under labeled storage range of 15-25°C (59-77°F).



Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA submission has provided adequate information on the chemistry, manufacturing and controls for the production of Istalol® (timolol maleate ophthalmic solution, 0.5%).

Except a few minor differences (discuss in the previous section), the overall manufacturing process in Bausch & Lomb is similar to [redacted]. Adequate in process tests and controls are included. The batch analysis has shown consistent results among the studied batches which indicates a consistent quality among the manufactured batches in Busch & Lomb. As far as the drug product specification is concerned, the applicant has implemented (for most of the tests attributes) the previously recommended acceptance criteria by the FDA. These include; tightening of the impurities acceptance criteria and also tightening of the benzalkonium assay in the shelf life specification (from [redacted]).

[redacted] The change in the supplier of the container/closure from [redacted] does not seem to have an impact on overall integrity of the packaging system [redacted]. [redacted] are the same. Moreover, the results of the water loss studies are comparable between the containers manufactured by the above mentioned suppliers. The submitted stability data support the proposed expiration dating period of 24 months for this product. Furthermore, the inspection results for all requested sites have been acceptable by the Office of Compliance.

**III Administrative**

**A. Reviewer's Signature**

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

**B. Endorsement Block**

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

32 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**NDA 21-516**

**ISTALOL<sup>®</sup>**  
**(timolol maleate ophthalmic solution, 0.5%)**

**Senju Pharmaceutical Co., Ltd**

**Hossein S. Khorshidi**  
**Division of Anti-Inflammatory/Analgesics & Ophthalmic**  
**Drug Products**  
**HFD-550**



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# Chemistry Review Data Sheet

1. NDA # **21-516**

2. REVIEW # 1

3. REVIEW DATE: 5/28/03

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	9/25/02
Amendment	12/17/02
Amendment	1/23/03
Amendment	1/9/03
Amendment	2/14/03
Amendment	4/23/03

7. NAME & ADDRESS OF APPLICANT:

Name: Senju Pharmaceutical Co., Ltd  
c/o PharmaLogic Development, Inc.

Address: 17 Bridgegate Drive  
San Rafael, CA 94903

Representative: Gary D. Novak, Ph.D.

Telephone: 415-472-2183



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Istalol<sup>®</sup> (timolol maleate ophthalmic solution), 0.5%
- b) Non-Proprietary Name (USAN): Timolol Maleate USP
- c) Code Name/# (138):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of ocular hypertension or open-angle glaucoma.

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

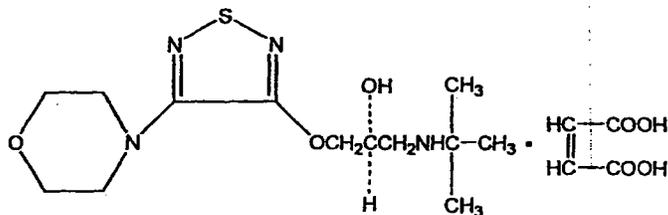
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet



$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$   
 Molecular Wt. 432.49

2-Propanol, [(1,1-dimethylethyl)amino]-3-[(4-(4-morpholinyl)-1,2,5-thiadiazole-3-yl)oxy]-, (S)-, (Z)-2-butenedioate(1:1) (salt)

**Other chemical name:**

(-)-1(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazole-3-yl)oxy]-2-propanol maleate (1:1) (salt).

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	II			3	Adequate	6/25/02	
2	II			1	Adequate	12/15/02	
3	III			3	Adequate	3/1/02 10/1/02	
4	III			3	Adequate	3/27/02	
5	III			1	Adequate	2/12/03	



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-086	Timoptic®(timolol maleate) Solution
ANDA	74-466	Timolol Maleate Ophthalmic solution, 0.5% USP
ANDA	74-516	Timolol Maleate Ophthalmic solution, 0.5% USP

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending	7/8/03	Hossein Khorshidi
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending	7/8/03	
OPDRA			
EA	Exclusion not accepted	7/8/03	Hossein Khorshidi
Microbiology	Pending	7/8/03	Stephene Langille

# The Chemistry Review for NDA # 21-516

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommended for Not Approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not at this time

### II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(2). Senju Pharmaceutical has not performed an extensive clinical trials for this product. The company has relied on the Agency's previous finding of safety and efficacy for the listed drugs as well as published clinical studies performed with similar marketed products, for exp., Timoptic® (NDA 18-086) solution and other generic brands including; ANDAs 74-466 and 74-516, Timolol Maleate Ophthalmic Solution. The proposed product is covered by U.S. patent No. 6,335,335

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### *Drug Substance:*

Timolol Maleate, USP (CAS No. 26921-17-5) are manufactured by [redacted] (DMF # [redacted]) and [redacted] (DMF # [redacted]), respectively. According to the applicant, [redacted] is considered as the primary source and the [redacted] as a secondary supplier. Both DMFs were reviewed and found to be adequate in support of NDA 21-516.

##### *Drug product:*

The proposed formulation is similar to the generic timolol maleate ophthalmic solution with exception that in the new formulation, potassium sorbate is used. The results of studies demonstrated that sorbic acid can facilitate the absorption of timolol into the aqueous humor by increasing the lipophilicity of timolol by ion-pairing formation.

The bulk solution for the stability batches was compounded at [redacted] and [redacted] batch sizes. An [redacted] batch size is proposed for commercialization of this product.

Executive Summary Section

Manufacturing process consists of [ ] appropriate in-process tests/controls for appearance, pH, osmolality, assay, benzalkonium chloride and potassium sorbate are included.

Drug product specification is deficient at this time. For example, for ID test, either one specific or two non-specific tests should be included. Acceptance criteria for the impurities have not resolved yet.

The formulation contain [ ] overage of the benzalkonium chloride. Data demonstrated [ ] Applicant has already addressed some of the problem [ ]

[ ] overage of [ ] as well as [ ] may be needed to address [ ]

Analytical methods and the validation data are described in details. Adequate stability protocols and supporting data are submitted. Applicant has proposed two packaging configurations for the commercial marketing of this product; 2.5 ml [ ] LDPE bottle and 5.0 ml fill/10 cc LDPE bottle respectively. For the larger fill size (5 ml fill), adequate stability data (— months of long term, — months of accelerated conditions on three batches of the drug products and — months of intermediate and refrigerated conditions on one batch) are provided. However, and for the [ ] size, data from only one batch are submitted at long term and accelerated stability conditions. “According to ICH Q1AR guidance, data from 3 batches for each proposed configuration for marketing should be submitted at time of NDA filing.”

The proposed container/closure is a white LDPE bottle with yellow cap and white tip. LOA to reference all relevant DMFs are provided. All DMFs reviewed and found to be adequate in support of NDA 21-516.

**B. Description of How the Drug Product is Intended to be Used**

Istalol® (timolol maleate ophthalmic solution, 0.5%) is a preserved, multi-dose solution of timolol maleate containing potassium sorbate. The drug is used topically. Recommended dose is one drop in the affected eye(s) once a day. According to the package insert, if the patient’s intraocular pressure is not a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. Product is recommended to be stored at 5-30°C (41-86°F). Based on provided stability data, applicant has proposed 24 months of expiry under labeled storage range of 5 to 30°C.



Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA submission has provided inadequate information on the chemistry, manufacturing and controls for the production of Istalol® (timolol maleate ophthalmic solution, 0.5%).

\* Applicant has not responded to the FDA's chemistry questions # 3,5,6 and 9 which were forwarded on 2/26/03. For example, in master batch record, the total manufacturing time [ ] is not specified. As far as the drug product specification is concerned, certain deficiencies are still existing, e.g., "one specific or two non specific tests for identification should be included. Acceptance criteria for the impurities are inadequate. Acceptance criteria for the benzalkonium chloride assay should be tightened at the shelf life, A limit of quantitation of [ ] should be included as part of system suitability test for HPLC analytical procedure # [ ]

\* Insufficient stability data are submitted for the proposed [ ] container size. Data from one batch (instead of three batches) are provided.

\* Applicant's request for the exemption from the environmental assessment has not been supported by adequate supporting data. It is not clear that how many batches of the drug products are expected to be manufactured per year and what would be the expected introduction concentration (EIC) of the drug substance at the point of entry into the aquatic environment.

\* According to the office of compliance, the inspection status of the [ ] (manufacturer of the drug product) is "withhold" at this time. A form 483 was issued.

**III Administrative**

**A. Reviewer's Signature**

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

**B. Endorsement Block**

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

55 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling