

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number     20-963**

**CHEMISTRY REVIEW(S)**

Division of Anti-inflammatory, Analgesic  
and Ophthalmic Drug Products  
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-963

DATE REVIEWED: September 2, 1998

REVIEW #: 1

REVIEWER: Rajendra Upoor, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
INITIAL NDA, N-000	16-FEB-98	18-FEB-98	24-FEB-98
AMENDMENT, NC	18-MAR-98	24-MAR-98	30-MAR-98
AMENDMENT, BC	25-MAR-98	02-APR-98	07-APR-98
AMENDMENT, BI	28-MAY-98	01-JUN-98	05-JUN-98
AMENDMENT, BC	14-JUL-98	15-JUL-98	22-JUL-98

NAME & ADDRESS OF APPLICANT:

Alcon Laboratories, Inc.  
6201 South Freeway  
Fort Worth, Texas 76134-2099.

DRUG PRODUCT NAME

Trade Name: Timolol Maleate Ophthalmic Gel Forming Solution, USP.  
(see page 2-001 of NDA).

Established: Timolol Maleate.

Code Name/#: FID 92376 for 0.25%, and FID 92316 for 0.5%.

Chem.Type/Ther.Class: 3S.

PHARMACOL. CATEGORY: Treatment of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma.

DOSAGE FORM: Ophthalmic Solution.

STRENGTHS: 0.25% and 0.5%.

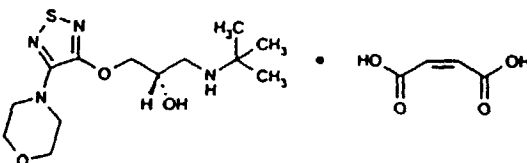
ROUTE OF ADMINISTRATION: Ophthalmic Drops.

DISPENSED:  X  Rx       OTC

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT,  
AND STRUCTURAL FORMULA:

2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (S)-, (Z)-2-butene-dioate (1:1) (salt); or

(-)-1-(tert-butylamino)-3-[[4-morpholino-1,2,5-thiadiazol-3-yl]oxy]-2-propanol maleate (1:1) (salt).  $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ . 432.40.



It is suggested that the following two items should be included in the manufacturing batch records:

- a. Supplemental Formulation Page should be included in the Bulk Product Order Form for the preparation of stock solution.
- b. Inclusion of a data entry space for noting the delivered to the stock solution during compounding.

**APPEARS THIS WAY  
ON ORIGINAL**

**Division of Anti-inflammatory, Analgesic  
and Ophthalmic Drug Products  
Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-963

**DATE REVIEWED:** October 15, 1998

**CHEM. REVIEW #:** 2

**REVIEWER:** Rajendra Upoor, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
INITIAL NDA, N-000	16-FEB-98	18-FEB-98	24-FEB-98
AMENDMENT, NC	18-MAR-98	24-MAR-98	30-MAR-98
AMENDMENT, BC	25-MAR-98	02-APR-98	07-APR-98
AMENDMENT, BI	28-MAY-98	01-JUN-98	05-JUN-98
AMENDMENT, BC	14-JUL-98	15-JUL-98	22-JUL-98

**Subject of this review:**

AMENDMENT, BZ	29-SEP-98	30-SEP-98	30-SEP-98
AMENDMENT, Fax	09-OCT-98	Not in COMIS until date above.	09-OCT-98
AMENDMENT	13-OCT-98	14-OCT-98	14-OCT-98

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Alcon Laboratories, Inc.  
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Fort Worth, Texas 76134-2099.

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**DOSAGE FORM:** Ophthalmic Solution.

**STRENGTHS:** 0.25% and 0.5%.

**ROUTE OF ADMINISTRATION:** Ophthalmic Drops.

**DISPENSED:**   X   Rx        OTC

**CHEMICAL NAME, MOLECULAR FORMULA, and MOLECULAR WEIGHT:**

2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (S)-, (Z)-2-butene-dioate (1:1) (salt); or (-)-1-(tert-butylamino)-3-[[4-(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt).  $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ . 432.50.  
See Timolol, USP 23, page 1553 for structural formula.

CONSULTS:

ONDC Microbiology Team Conclusion: Microbiologist's Review # 3 dated September 17, 1998 recommends APPROVAL for the sterility assurance issues provided in this application.

REMARKS:

List of CMC comments and recommendations that should be sent to the applicant for response are given on page 15 of this chemistry review.

CONCLUSIONS & RECOMMENDATIONS:

The product can be given a shelf-life of 18 months at this time. From the chemistry stand point, this application is recommended for an approvable action. Please refer to the list of CMC comments on page 15 of this review that should be communicated to the applicant for their consideration and response.

cc:

Orig. NDA 20-963.  
HFD-550/Division File.  
HFD-550/R.Uppoor.  
HFD-550/CSO/L.Gorski.  
HFD-550/MO/W.Chambers.  
HFD-550/PharmTox/A.Weir.  
HFD-805/Micro/P.Stinavage  
HFD-550/Chem.TL/H.Patel  
HFD-550/Chem.TL/L.Ng  
HFD-830/DD/C-w.Chen

*U. Rajendra* 10/19/1998  
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**APPEARS THIS WAY  
ON ORIGINAL**