CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-963

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Desk Copy

Airbome Express No.
8383744655

Alcon LABORATORIES

February 23, 1998

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Scott Krueger
Director, Regulatory Affairs

Ms. Lori Gorski
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-963
Timolol Maleate Gel Forming Solution
Electronic Desk Copy

Dear Ms. Gorski:

As discussed in the cover letter to the original submission and in our follow-up telephone conversation, please find enclosed the following desk copies presented on three separate CD-ROMs.

- One CD-ROM containing word processing files; said files encompass Part 2 (Labeling); Part 3 (Summaries) and Part 8 (Clinical) in WORD 6, WORD 8 or WordPerfect 5.1 format. Please see the attached "Read Me" file.
- One CD-ROM containing patient listings for Protocols C-97-03 and C-97-04 in EXCEL.
- One CD-ROM with SAS Programs and Data Sets for Protocols C-97-03 and C-97-04. A hard copy of Annotated CRF's for these studies is also provided.

If you have any questions or comments concerning these desk copies, please contact me at (817) 551-8512.

Sincerely,

Scott Krueger,
Director

SK/bw

Desk Copy: Ms. Lori Gorski

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314 & 601)

Form approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon Laboratories, Inc.	**02/23/98**
TELEPHONE NO. *(Include Area Code)* **(817) 568-6296**	FACSIMILE (FAX) Number *(Include Area Code)* **(817) 551-4630**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: **6201 South Freeway Fort Worth, Texas 76134 - 2099**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously used) NDA 20-963

ESTABLISHED NAME *(e.g., Proper Name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Timolol Maleate	**Timolol Maleate Gel Forming Solution**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)* | CODE NAME *(if any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	**0.25%, 0.5%**	**Topical (ocular)**

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NC
NEW CORRESP
~~ORIGINAL~~
DUPLICATE

Alcon LABORATORIES

Certified Mail Z 047 938 860
Return Receipt Requested

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Scott Krueger
Director, Regulatory Affairs

February 25, 1998

Ms. Lori Gorski
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-963
Timolol Maleate Ophthalmic Gel Forming Solution
Revised 356h Form

Dear Ms. Gorski:

Per your request, please find attached a 356h form which has been revised to reflect the indication being sought for this submission and to add the IND number to the cross-references.

If you require any additional information, please contact me at (817) 551-8512.

Sincerely,

Scott Krueger
Director

SK/bw
enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314 & 601)

Form approved: [illegible]
Expiration Date: [illegible], 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon Laboratories, Inc.	02/16/98
TELEPHONE NO. *(Include Area Code)* (817) 568-6296	FACSIMILE (FAX) Number *(Include Area Code)* (817) 551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 6201 South Freeway, Fort Worth, Texas 76134 - 2099	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously used) NDA 20-963

ESTABLISHED NAME *(e.g., Proper Name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Timolol Maleate	Timolol Maleate Ophthalmic Gel Forming Solution

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.25%, 0.5%	Topical (ocular)

(PROPOSED) INDICATION(S) FOR USE:
Treatment of elevated intraocular pressure.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

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Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 33 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NDA: 18-086, 18-017, 20-330. IND: 52-197. ANDA: 74-261, 74-262
DMF: 8226, 7264, 1528, 2044, 1466, 2392, 3567.

HFD-550 Gorski

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-963

MAR 3 1998

Alcon Laboratories
Attention: Scott Krueger
Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Mr. Krueger:

We received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Timolol Maleate (timolol maleate ophthalmic gel forming solution) Ophthalmic Gel Forming Solution 0.25% & 0.5%
Therapeutic Classification:	Standard
Date of Application:	February 16, 1998
Our Reference Number:	NDA 20-963

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 with be filed under section 505(b)(2) of the Act on April 17, 1998, in accordance with 21 CFR 314.101(a).

Should you have any questions, please call Lori Gorski, Project Manager, (301) 827-2090.

Please site the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

CAK 3/3/98

Chin Koerner
Acting Supervisory Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 20-963
HFD-550/Div. files
HFD-550/Acting SPMS/Koerner
HFD-550/MO/Chambers
HFD-550/CSO/Gorski

Drafted by: lmg/Feb 24, 1998/n:\gorski\nda\alcon\20963.ack

March 18, 1998

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

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Re: NDA 20-963
TIMOLOL GEL FORMING OPHTHALMIC SOLUTION
Amendment to Pending Application

Dear Madam or Sir,

On March 13, 1998, Lori Gorski, Project Manager, requested that contact information for the manufacturers/suppliers included in the application be summarized. Following please find a tabulated summary of the contact information for the manufacturers/suppliers cited in the above referenced application filed February 16, 1998.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Fax Copy to: Lori Gorski, Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314 & 601)

Form approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon Laboratories, Inc.	03/18/98
TELEPHONE NO. *(Include Area Code)* (817) 568-4325	FACSIMILE (FAX) Number *(Include Area Code)* (817) 551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 6201 South Freeway - R7-18 Fort Worth, Texas 76134	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously used) NDA 20-963

ESTABLISHED NAME *(e.g., Proper Name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
	Timolol Maleate Ophthalmic Gel Forming Solution, 0.25% & 0.5%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.25% and 0.5%	Topical (Ocular)

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Amendment

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, and [illegible] conducted at each site. Please indicate whether each site is ready for inspection, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306(k)(1))
	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Amendment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Cheryl B. Anderson Manager Regulatory Affairs	03/18/98

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway - R7-18, Fort Worth, Texas 76134	(817) 568-4325

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to the address

March 25, 1998

BC

ORIG AMENDMENT

ORIGINAL

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

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

Re: NDA 20-963
TIMOLOL GEL FORMING OPHTHALMIC SOLUTION
Amendment to Pending Application

Dear Madam or Sir,

A request was made by Lori Gorski, Project Manager, for additional contact information for the raw material suppliers. Following please find an updated tabulated summary of the contact information for the manufacturers/suppliers cited in the above referenced application filed February 16, 1998.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

April 14, 1998

SU
DUPLICATE

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

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

Re: NDA 20-963
Timolol Gel Forming Solution
Response to Request for Information

Dear Ms. Gorski,

In a telephone conference with Dr. Richard Gural, Dr. Chambers requested additional information. Per Dr. Chamber's request, the information below is provided.

1. Updated six-month safety report for **all** enrolled patients for protocol C-97-05 (long-term study). Baseline demographics and baseline IOP values for all enrolled patients are included.
2. Reanalysis of the primary efficacy data using **IOP change from baseline** for all patients including the intent-to-treat group for clinical protocols C-97-03 and C-97-04. The results show that all treatment differences ≤ 0.7 mm Hg and upper 95% confidence interval ≤1.44 mm Hg at all peak and trough time points across the three month treatment period.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325 or Scott Krueger at (817) 568-6116.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk Copies: Lori Gorski, Project Manager

Airborne Airbill
#5278766220

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
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NAME OF APPLICANT	DATE OF SUBMISSION
Alcon Laboratories, Inc.	04/14/98
TELEPHONE NO. *(Include Area Code)* (817) 551-4325	FACSIMILE (FAX) Number *(Include Area Code)* (817) 551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 6201 South Freeway - R7-18, Ft. Worth, TX 76134	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously used) NDA 20-963

ESTABLISHED NAME *(e.g., Proper Name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Timolol Gel Forming Solution	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)* | CODE NAME *(if any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.25%, 0.5%	Topical (ocular)

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	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
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	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
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	16. Debarment certification (FD&C Act 306(k)(1))
	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlege are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Cheryl B. Anderson	Cheryl B. Anderson, Pharm.D. Manager, Regulatory Affairs	04/14/98

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway - R7-18, Ft. Worth, TX 76134	(817)551-4325

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

Please DO NOT RETURN this form to this address.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

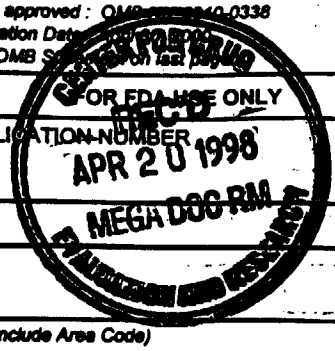
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314 & 601)

Form approved : OMB [illegible]-0338
Expiration Date: [illegible] 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER



APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon Laboratories, Inc.	04/17/98
TELEPHONE NO. *(Include Area Code)* (817) 551-4325	FACSIMILE (FAX) Number *(Include Area Code)* (817) 551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 6201 South Freeway - R7-18, Ft. Worth, TX 76134	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously used) NDA 20-963

ESTABLISHED NAME *(e.g., Proper Name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Timolol Gel Forming Solution	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)* | CODE NAME *(if any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.25%, 0.5%	Topical (ocular)

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug | Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

May 28, 1998

BL
ORIGINAL

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

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

Re: NDA 20-963
TIMOLOL GEL FORMING OPHTHALMIC SOLUTION, 0.25% & 0.5%
Amendment to Pending Application

Dear Madam or Sir,

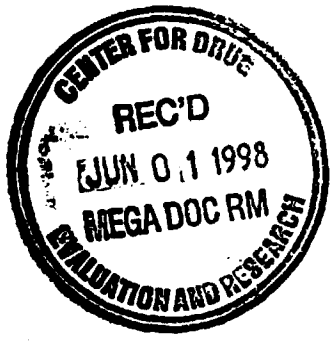
Reference is made to FDA facsimile communication dated April 14, 1998. The Agency requested a response to microbiological issues concerning sterility assurance. Following you will find our response. A copy of the FDA communication is provided to facilitate the review.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk Copy: Lori Gorski, Project Manager



Airborne Airbill
#527 876 8526

July 2, 1998

Alcon

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

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

Re: NDA 20-963
Timolol Gel Forming Ophthalmic Solution, 0.25% and 0.5%
Four Month Safety Update

Dear Madam or Sir,

Please find enclosed the Four Month Safety Update Report for the above referenced NDA which was submitted February 18, 1998. The data lockpoint for this report is May 29, 1998. An Archival and Clinical review copy are provided. In addition, a desk copy for the pharmacology/toxicology review.

An electronic copy in Microsoft Word v. 6.0/95 is provided with the clinical review copy.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk copy to: Lori Gorski, Project Manager

Via Airborne Express 2075634875

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

July 14, 1998

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

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

Re: NDA 20-963
Timolol Gel Forming Solution, 0.25% and 0.5%
Amendment to Pending Application – Stability Update

Dear Madam or Sir,

The above referenced application was submitted to the FDA on February 16, 1998. Enclosed you will find an updated stability report that includes 52 weeks of stability data at room temperature. Alcon proposes that the expiration dating be extended from 12 months to 18 months based on these data.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Desk Copy: Lori Gorski

Desk Copy

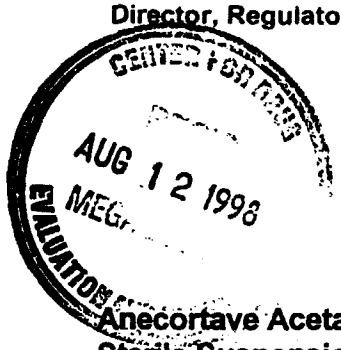
Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

August 11, 1998

Ms. Lori Gorski
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

Scott Krueger
Director, Regulatory Affairs



RE: NDA 20-963
Timolol Gel Forming Solution and Anecortave Acetate
Video Tape Sterile Suspension
Desk Copies of IND

Dear Ms. Gorski:

In follow-up to our telephone discussion, please find enclosed a video tape which demonstrates the gelation of Timolol Gel Forming Solution upon the addition of

Also enclosed is the remainder of the for your desk copy, Items 5, 6, 7, 8, and 9.

If you have any questions concerning the tape or the IND, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Director, Regulatory Affairs

SK/bw
enclosure
Airborne Express No. 2075635575

Certified Mail
Z-047-939-537

DUPLICATE

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

August 18, 1998

Ms. Lori Gorski
Division of Analgesic, Anti-Inflammatory
And Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-963
Timolol Maleate Ophthalmic Gel
Forming Solution, 0.25% and 0.5%
Response to Request for Information and Revised Labeling

Dear Ms. Gorski,

Please find enclosed our responses to the additional clinical issues and the request for revised labeling presented in your telefax of August 10,1998. Our responses to the clinical issues are presented as Attachment I to this letter.

The revised labeling (Attachment II) differs from the text suggested in your August 10 fax in the following elements. These modifications have been reviewed with Dr. Chambers.

1. In the *Information for Patients* section, the suggested statement **"Transient blurred vision, generally lasting from 30 seconds to 5 minutes, following installation, and potential visual disturbances may impair the ability to perform hazardous tasks such as operating machinery or driving a motor vehicle."** has been modified to state **"Transient blurred vision or visual disturbance, generally lasting from 30 seconds to 5 minutes, following instillation may impair the ability to perform hazardous tasks such as operating machinery or driving a motor vehicle."**

2. In the **ADVERSE REACTIONS** section, the suggested statement: **"The frequency of patients reporting burning and stinging upon instillation was approximately one in eight patients."** has been modified to reflect that this incidence was comparable to that observed for TIMOPTIC. This is accomplished by the following statement: **"The frequency of patients reporting burning and stinging upon instillation was approximately one in eight patients which was comparable to that observed for TIMOPTIC."**

3. In the **Storage** section, the statement "Avoid Freezing." has been deleted. Our freeze/thaw stability data demonstrate that the formulation is not sensitive to freeze/thaw conditions. The NDA references to the data supporting this deletion are presented in Attachment III.

Also, in response to your telephone conversation of July 16, 1998 with Dr. Anderson concerning cap color for Timolol Maleate Gel Forming Solution, Alcon agrees to utilize the "yellow" cap color for both the 0.5% and 0.25% concentrations in domestically marketed product. It is our understanding that additional information is not required to support this change based upon already submitted information.

If you have any questions or comments concerning this response, please do not hesitate to contact me. .

Sincerely,

Scott Krueger

Desk Copy: Lori Gorski (2 copies)
Airborne #207-563-5774

Airborne Airbill 2075636275

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Scott Krueger
Director, Regulatory Affairs

August 25, 1998

Ms. Lori Gorski
Project Manager
DAAODP, HFD-550
Food and Drug Administration
Central Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 20-963
Timolol Maleate Gel Forming Solution 0.25% and 0.5%
Final Revised Labeling

Dear Ms. Gorski,

Please find attached the revised final insert text for Timolol Maleate Gel Forming Solution. This revision incorporates the changes which were requested in our teleconference of August 24, 1998.

If you have any questions or comments concerning this submission, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Director, Regulatory Affairs

SK/bw/tgfs/labeling.doc

September 29, 1998

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Scott Krueger
Director, Regulatory Affairs

Ms. Lori Gorski
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-963
Timolol Maleate Ophthalmic Gel Forming Solution
Response to Request for Information

Dear Ms. Gorski:

Please find enclosed our responses to the request for information presented by the Chemistry Reviewer in your telefax of September 4 (Section 1) and the comment from the Pharmacokinetic Reviewer in your telefax of September 8 (Section 2).

In addition, as discussed in teleconference with Dr. Chambers and yourself on September 18, included in Section 3 is Alcon's commitment to conduct a reanalysis of Protocol C-97-04 without investigator #1237.

Final draft labeling is provided as the response to the Chemists issue #1. The temperature statement has been corrected. Other changes from the previous version affect only the How Supplied Section and reflect the inclusion of the NDC numbers.

If you have any questions or comments regarding these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Director, Regulatory Affairs

SK/bw/enclosures
Airborne Express 2075637476

NDA ORIG AMENDMENT

October 9, 1998 BC

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Ms Lori Gorski
Division of Analgesic, Anti-inflammatory and
Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

Scott Krueger
Director, Regulat[illegible]

RE: NDA 20-963
Timolol Maleate Ophthalmic Gel Forming Solution
Response to Request for Information

Dear Ms. Gorski,

In our teleconference of October 2, 1998, Dr. Chambers requested acetate data be generated to correspond with some of the later gel strength measurements at 40°C and 25°C. This has been done. Please find attached the revised plots plots (Figure 2-1 and 2-2) and tables (Table 2-1) containing the additional measurements requested by Dr. Chambers.

If you have any questions or comments concerning these data, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger

Scott Krueger

Certified Mail Z 215 459 764

October 13, 1998

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Scott Krueger
Director, Regulatory Affairs

Dr. Chambers
Division of Analgesic, Anti-inflammatory and
Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-963
Timolol Maleate Ophthalmic Gel Forming Solution
Response to Request for Information

Dear Dr. Chambers,

In response to our discussion of October 9, 1998, I am pleased to provide you with a copy of the revised labeling which makes the following requested editorial corrections.

1. In the first sentence of paragraph 2 on Page 2 of the insert, a comma has been inserted following the word "normal". The sentence now reads "... of reducing elevated, as well as normal, intraocular pressure, ...".
2. The legend to the figures presenting the Mean IOP data for the 0.25% study have been revised to correctly identify the study drugs as being the 0.25% concentration.
3. In the last paragraph of the Adverse Reactions section discussing clinical experience with oral timolol maleate, "neuropsychometrics tests" was revised to read "neuropsychometric tests".

Furthermore, in reviewing the draft labeling for the carton and container, I discovered that the product name was presented incorrectly as "Timolol Maleate Gel Forming Ophthalmic Solution." The name has been corrected to "Timolol Maleate Ophthalmic Gel Forming Solution." Revised draft labeling making this correction is also provided.

In addition, Alcon Laboratories Inc., agrees to accept the following modifications of our CMC submission:

1. Alcon agrees to revise the specification limits for benzododecinium bromide in the drug product to be of label.

2. Alcon agrees to modify our stability protocol commitment of September 29, 1998. Alcon has revised the testing performed on inverted stability samples to be consistent with the tests for upright storage.

If you have any questions concerning the provided information, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Director, Regulatory Affairs

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Direct Line: (817) 551-3066
Telefax No: (817) 551-4610

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED
No. P 881 590 196 [Merck & Co., Inc.]
No. P 881 590 197 [Merck Research Laboratories]

April 9, 1998

Merck & Co., Inc.
Attn: Sylvia A. Ayler
P. O. Box 20000
R460-30
Rahway, NJ 07065-0907

Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

Re: U.S. Patent No. 4,861,760

Dear Sirs:

The above-referenced patent is identified in the Orange Book as covering Merck & Co., Inc.'s Timoptic-XE™ (timolol maleate ophthalmic gel forming solution) product. Pursuant to Section 505(b)(3)B of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b)(3)(B)), the purpose of this letter is to notify Merck & Co., Inc. ("Merck"), as a representative of the owner of the subject patent (Chibret International, SA) and Merck Research Laboratories, as holder of the approved application, that a 505(b)(2) application directed to a timolol maleate ophthalmic gel forming solution product has been submitted by Alcon and has been filed by the United States Food and Drug Administration (FDA).

The FDA has acknowledged receipt of Alcon's 505(b)(2) NDA directed to a timolol maleate ophthalmic gel forming solution product. The number assigned to Alcon's 505(b)(2) NDA by the FDA is NDA 20-963.

The established name of the proposed drug product is Timolol Maleate Ophthalmic Gel Forming Solution 0.25% and 0.5% (hereinafter referred to as "Alcon's Proposed Product").

The active ingredient in Alcon's Proposed Product is timolol maleate, present at a concentration of 0.34% or 0.68% by weight (equivalent to 0.25 or 0.5% by weight timolol, respectively). Alcon's Proposed Product is formulated as a topically administrable gel forming aqueous solution.

The patent which Alcon has certified will not be infringed by Alcon's Proposed Product is U.S. Patent No. 4,861,760 ("the '760 patent"), which expires on September 25, 2006.

The factual and legal grounds for Alcon's certification of noninfringement of the '760 patent are as follows.

The '760 patent contains only one independent claim (Claim 1). This claim recites a liquid aqueous ophthalmological composition which on administration to the eye changes from a liquid to a gel as a result of the ionic strength of the lacrimal fluid. The claimed composition comprises 0.1 to 2% by weight of gellan gum as an essential ingredient.

The specification describes the invention as a composition "intended for contacting with a physiological liquid ... this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling in situ under the effect of an increase in the ionic strength of said physiological liquid." ('760 patent, Col. 2, lines 16 - 24). The '760 patent makes it very clear that the liquid-gel phase transition occurs due to a change in ionic strength and "[t]o this end, the total ionic strength of the formulation must be kept as low as possible" in order to facilitate the liquid-gel phase transition ('760 patent, Col. 7, lines 1 - 2). The '760 patent identifies polysaccharides "obtained by fermentation of a microorganism" as especially suitable for use in the compositions of the invention, but only specifically identifies one such polysaccharide, gellan gum ('760 patent, Col. 3, lines 7 - 41).

When the application that eventually resulted in the '760 patent was filed in the U.S. Patent and Trademark Office, it contained claims much broader in scope than the issued claims. Specifically, Claim 1 of the application originally read as follows:

> 1. Pharmaceutical composition intended for contacting with a physiological liquid characterized in that said composition is intended to be administered as a non-gelled liquid form and is intended to gel in situ, this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling in situ under the effect of an increase in the ionic strength of said physiological liquid.

This claim was rejected based upon prior art. The prior art references cited against the application were characterized by the Examiner as disclosing (1) pharmaceutical compositions containing polysaccharides obtainable by fermentation of microorganisms, where the compositions form gels in the presence of ionic solutions; (2) ophthalmic compositions containing polysaccharides, including the concept of a gelable polysaccharide; and (3) gelable compositions containing polysaccharides obtainable by fermentation of Pseudomonas elodea (i.e., gellan gum). During prosecution of the application, in response to rejections based upon prior art, the claim was significantly amended to specify that the composition was an ophthalmic composition, the concentration of polysaccharide was 0.1 - 2% by weight, and the identity of the polysaccharide was gellan gum. In order to obtain the '760 patent, Merck distinguished gellan gum from the other polysaccharides (e.g., xanthan gum) disclosed in the references cited by the Examiner and argued that none of the references suggested the use of gellan gum in an ophthalmic composition.

The most reasonable conclusion that can be drawn from the prosecution history of the '760 patent is that the patentee established, to the Examiner's satisfaction, the criticality of gellan gum in ophthalmic compositions. As a corollary, it may also be concluded that without the restriction of the claims to gellan gum only, the '760 patent would not have issued. Accordingly, the claims of the '760 patent are limited to ophthalmic compositions containing gellan gum, and cannot be construed as covering ophthalmic compositions that do not contain gellan gum. The broader features of the invention disclosed in the patent specification, but not claimed, are dedicated to the public. Maxwell v. J. Baker, Inc., 86 F.3d 1098, 1106-07, 39 USPQ2d 1001 (Fed. Cir. 1996), cert. denied 117 S.Ct. 1244, (1997).

It is well-settled that patent infringement requires the presence of every claim element or its substantial equivalent in the accused product. Perkin-Elmer v. Westinghouse Elec. Corp., 822 F.2d 1528,1533, 3 USPQ 2d 1321, 1324-25 (Fed. Cir. 1987). See also, e.g., Sofmaor Danek Group, Inc. v. DePuy-Motch, Inc., 74 F.3d 1216, 1220, 27 USPQ 2d 1529 (Fed. Cir. 1996); Dolly, Inc. v. Spalding & C Evenflo Cos., Inc., 16 F.3d 394, 397, 29 USPQ 2d 1767 (Fed. Cir. 1994); Miles Laboratories, Inc. v. Shandon, Inc., 997 F.2d 870, 876, 27 USPQ 2d 1123 (Fed. Cir. 1993). It is thus equally well-settled that failure to meet a single limitation is sufficient to negate an allegation of infringement. See, e.g., *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1583, 1535, 19 USPQ 2d 1367, 1369 (Fed. Cir. 1991). See, also the cases collected in Lipscomb's Walker on Patents, Third Edition, Vol. 6, Section 22:31, (1987), and cumulative supplement thereto (1993). Thus, the Court of Appeals for the Federal Circuit, in *Becton Dickenson & Co. v. C. R. Bard, Inc.*, 922 F.2d 792, 798, 17 USPQ 2d 1097, 1101 (Fed.Cir., 1990) acknowledged the patentee's assertion that some of the claim limitations were not necessary to achieve the claimed result. Nevertheless, the court explained:

> That may be true, but limitations of the axial extent of the jacket and the forming of an extension of the spring appear to have been necessary for patentability. But whether necessary or not, after issuance, all limitations in a claim are material and must be met exactly or equivalently in an accused device to find that the accused device works in the same way. Id.: *Corning Glass Works*, 868 F.2d 1259, 9 USPQ 2d 1968; *Lemelson v. United States*, 752 F.2d 1538, 1551, 224 USPQ 526, 533 (Fed. Cir., 1985)." (Emphasis added)

Also see *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 20 USPQ 2d 1456 (Fed. Cir., 1991), which cites the Becton Dickinson case with approval. The rule requiring the presence of every claimed element in the accused product is unaffected by the doctrine of equivalents, which "is not a license to ignore or erase ... structural and functional limitations of the claim, limitations on which the public is entitled to rely in avoiding infringement." Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1582, 37 USPQ 2d 1365 (Fed.Cir. 1996). The doctrine of equivalents is applied to every element of a claim, not to the invention as a whole. Warner-Jenkinson Co., v. Hilton Davis Chem. Co., 117S.Ct. 1040, 1049 (1997).

Moreover, the prosecution history of the '760 patent is relevant to the issue of infringement, not only for the purposes of determining whether prosecution history estoppel exists, but also for construing the meaning and scope of the claims. Alpex Computer Corp. v. Nintendo Co., Ltd., 102F.3d 1214, 40 USPQ 2d 1667 (Fed. Cir. 1996). As the Federal Circuit has explained, "[c]laim interpretation in view of the prosecution history is a preliminary step in determining literal infringement, while prosecution history estoppel applies as a limitation on the range of equivalents if, after the claims have been properly interpreted, no literal infringement has been found." Southwall Technologies, Inc. v. Cardinal IG Co., 54 F.3d 1570, 1578, 34 USPQ 2d 1673 (Fed. Cir. 1995). Moreover, prosecution history estoppel is a policy oriented limitation on the range of equivalents available to the patentee. *Loctite Corp. v. Ultraseal, Ltd.*, 782 F.2d 861, 870, 228 USPQ 90, 96 (Fed. Cir., 1985). "Prosecution history estoppel bars the patentee from recapturing subject matter that was surrendered by the patentee in order to promote allowance of the claims." Insituform Technologies, Inc. v. Cat Contracting, Inc., 99 F.3d 1098, 1107, 40 USPQ 2d 1602, 1609 (Fed. Cir. 1996), cert. denied, 117 S.Ct. 1555 (1997). See also Townsend Engineering Co. v. Hitec Co., Ltd., 829 F.2d 1086, 1090, 4 USPQ 2d 1136, 1140 (Fed. Cir. 1987). In the case of the '760 patent, the polysaccharides (e.g., xanthan gum) which Merck distinguished from gellan gum cannot be considered to be infringing equivalents.

Alcon's Proposed Product contains the following ingredients: Timolol Maleate, Xanthan Gum, Benzododecinium Bromide, Tromethamine, Boric Acid, Mannitol, Polysorbate 80 and Purified Water.

Alcon's Proposed Product contains xanthan gum, but does not contain gellan gum. Therefore, the only logical conclusion is that it would not infringe, either literally or substantively, Claim 1 of the '760 patent. Because Claims 2-8 of the '760 patent depend, directly or indirectly, from Claim 1, Alcon's Proposed Product would not infringe these claims either. See *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1552, n9, 10 USPQ 2d 1201, 1207, n9 (Fed.Cir., 1989).

For the foregoing reasons, namely (i) because Alcon's Proposed Product lacks a claimed element, gellan gum; and (ii) because the presence of gellan gum is shown by the prosecution history to have been an essential ingredient giving rise to patentability, Alcon's Proposed Product would not infringe the '760 patent either literally or under the doctrine of equivalents.

The foregoing product information and claim analysis are believed to provide an irrefutable basis for concluding that the Alcon Proposed Product does not infringe the claims of the '760 patent. In the event you believe that further information concerning the composition of Alcon's Proposed Product is required, however, please do not hesitate to contact me. Under an appropriate confidentiality agreement, Alcon is willing to disclose the concentration of each of the ingredients in the Alcon Proposed Product.

Sincerely,

Patrick M. Ryan

Patrick M. Ryan
Assistant General Counsel

April 17, 1998

N C
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Alcon
LABORATORIES

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

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Re: NDA 20-963
Timolol Gel Forming Solution
Amendment To Pending Application

Dear Madam or Sir,

Pursuant to the provisions of 21 CFR § 314.52(e), Alcon is amending its application to provide documentation of receipt of the notice of certification of noninfringement of a patent sent to Merck & Co., Inc. and Merck Research Laboratories [identified under paragraph (a) of this section] on April 9, 1998.

Based on the New Jersey postal stamp date, Merck & Co., Inc. received said notice on or before April 14, 1998. Merck Research Laboratories acknowledged receipt of said notice on 4/13/98. A copy of the certified mail receipts are appended.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Airborne Airbill
#5278766824

April 14, 1998

NC
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Division of Analgesic, Anti-Inflammatory and
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9201 Corporate Boulevard
Rockville, Maryland 20850

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6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Re: NDA 20-963
Timolol Gel Forming Solution
Amendment To Pending Application

Dear Madam or Sir,

Pursuant to the provisions of 21 CFR 314.52(b), Alcon is amending its application to certify that a notice has been provided to Merck & Co., Inc. [identified under paragraph (a) of this section] on April 9, 1998 (see attached). Alcon further certifies that the notice meets the content requirements under paragraph (c) of this section.

If you have any questions regarding the format or content of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

ALCON LABORATORIES, INC.

PARAGRAPH IV CERTIFICATION

Pursuant to section 505(b)(2)(A) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)(A)) ("the Act"), Alcon Laboratories, Inc. ("Alcon"), hereby certifies that, in its opinion and the best of its knowledge, United States Patent No. 4,861,760 ("the '760 patent") will not be infringed by the manufacture, use or sale of the Alcon Timolol Gel Forming Solution 0.25% and 0.5% for which this application is submitted. Pursuant to the requirements of 21 CFR 314.95(a) and 21 CFR 314.95(c), Alcon will provide notice of the submission of this application and a detailed statement of the factual and legal basis for Alcon's opinion that the '760 patent will not be infringed, to Merck & Co., Inc. (Attn: Sylvia A. Ayler), P. O. Box 20000, RY60-30, Rahway, NJ 07065-0907, the designated representative of the patent owner of record, Chibret International, SA, 3 Avenue Hoche, Paris France, F75008, and Merck Research Laboratories, Sumneytown Pike, West Point, PA, 19486, the holder of an approved application under section 505(b) of the Act.

Date: January 13, 1998

Alcon Laboratories, Inc.
James A. Arno
Vice President, Legal Counsel

APPEARS THIS WAY
ON ORIGINAL

14-002

ALCON LABORATORIES, INC.

PARAGRAPH II CERTIFICATION

Pursuant to section 505(b)(2)(A) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)(A)), Alcon Laboratories, Inc. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,195,085 assigned to Merck & Co., Inc. expired on March 25, 1997.

Date: January 13, 1998

Alcon Laboratories, Inc.
James A. Arno
Vice President, Legal Counsel

APPEARS THIS WAY
ON ORIGINAL

14-003

ITEM 13 **PATENT AND EXCLUSIVITY INFORMATION**

There are currently no patents for this product. Consistent with 21CFR §314.108(b)(4), Alcon Laboratories, Inc. requests a 3-year period of exclusivity following the approval of this 505(b)(2) application.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # NDA 20-963 SUPPL #_____

Trade Name Timolol Gel Forming Solution Generic Name Timolol Maleate Ophthalmic Gel Forming Solution

Applicant Name Alcon Laboratories HFD- 550

Approval Date, if known 10/21/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   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 /___/

   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 /___/

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

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /✓/ NO /___/

If yes, NDA # 20-330 Drug Name Timoptic-XE

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 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 /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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. 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 /___/

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:

_____

_____

YES /___/ NO /___/

(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 /___/

(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: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
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 _____
_____	_____
_____	_____
Investigation #2	
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: _____

_____

_____ 10/2/98

Signature Date

Title: Deputy Division Director

_____ _____

Signature of Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Add New Pediatric Information to this Submission

User Information

Preparer	LORI GORSKI
Title	PROJECT MANAGER/CONSUMER SAFETY OFFICER
Division	HFD-550

Application Information

Application Number	020963
Application Clock Date	1998-02-18 00:00:00
Application Type	N
Applicant Sponsor	ALCON
Drug Trade Name	TIMOLOL MALEATE OPHTHAL
Drug Generic Name	TIMOLOL MALEATE OPHTHAL
(leave supplement number, date and type blank, if original application)	
Supplement Number	
Supplement Date	
Supplement Type	
Proposed Indication(s)	Timolol Maleate (timolol maleate ophthalmi solution) Ophthalmic Gel Forming Solution, for the treatment of elevated intraocular pre with ocular hypertension or open-angle glau
Has Proposed Indication been Approved?	☒ Check for YES
Adequacy of proposed label for Pediatric Dosing	Does Not Apply
Regulatory Action	Approved
Is there a Pediatric Phase 4 Commitment in the Action Letter for the Original Submission?	☐ Check if YES
Comments & Recommendations (please date)	
Is there Pediatric Content in this Submission?	○ Yes ◉ No

Continue Clea

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ON ORIGINAL

ITEM 16. DEBARMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Alcon Laboratories, Inc. certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity in connection with this application the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

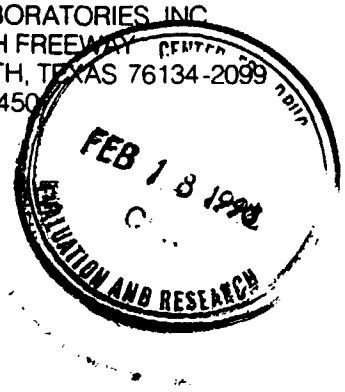
20963

Airborne Express Airbill 2672906364

February 16, 1998

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450



Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 20-963
Timolol Maleate Ophthalmic Gel
Forming Solution, 0.25% and 0.5%
Original New Drug Application – User Fee ID #3405

Dear Sir/Madam:

Pursuant to the provisions of Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and 21 CFR 314.54, a New Drug Application (NDA) for Timolol Maleate Ophthalmic Gel Forming Solution (0.25% and 0.5%) is hereby submitted. The drug product is an ophthalmic gel forming solution indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. The data and information presented within this application are consistent with our discussions at our End-of-Phase II meeting for held on January 16, 1997. These data demonstrate that 1) Alcon's Timolol Maleate Ophthalmic Gel Forming Solution is pharmaceutically equivalent to Merck's TIMOPTIC-XE® (timolol maleate ophthalmic gel forming solution; NDA 20-330); and 2) dosed once-per-day, is clinically equivalent to Merck's TIMOPTIC® (Timolol Maleate Ophthalmic Solution; NDA 18-086) dosed twice-daily. Accordingly, it is our understanding that demonstration of equivalency from these studies will result in the assignment of an "AB" therapeutic equivalency rating between Alcon's Timolol Maleate Ophthalmic Gel Forming Solution and TIMOPTIC-XE® in the Orange Book.

The majority of the preclinical and clinical information in support of the safety and efficacy of this drug product are based on published literature and studies conducted by Merck in support of TIMOPTIC-XE® Ophthalmic Gel Forming Solution (NDA 20-330), TIMOPTIC® Ophthalmic Solution (NDA 18-086) and BLOCADREN® tablets (NDA 18-017). The applicant is submitting the application under Section 505(b)(2) since the studies relied upon by the applicant were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the persons who conducted the investigations.

The Prescription Drug User Fee Act of 1992 and the Modernization Act of 1997 do not require an applicant to pay a fee for an application filed under Section 505(b)(2) unless the application is for a new chemical entity which is an active ingredient or an indication for a use that has not been approved under a Section 505(b) application. This 505(b)(2) application therefore does not require a user fee since timolol maleate, the active ingredient, is not a new molecular entity (approved in NDAs cited above). The indication for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma was also previously approved under NDA 18-086 and NDA 20-330.