CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-869

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 20-869 **SUPPL #**_____

Trade Name Cosopt **Generic Name** dorzolamide hydrochloride and timolol maleate

Applicant Name Merck **HFD-** 550

Approval Date, if known 4-7-98

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 /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   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 /X/ 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 /X/

If yes, NDA #_____ Drug Name _____

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 /X/

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 /X/ NO /___/

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

NDA# 20-408 Trusopt (dorzolamide HCl) [illegible]

NDA# [illegible] [illegible]

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 /X/ 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 /X/ 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 /X/

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

YES /___/ NO /___/

If yes, explain: _____

_____

(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 /X/

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:

Protocols 44, 47, 63, 64, 43, 58

_____

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 44 YES /___/ NO /X/

Investigation #2 47, 63, 64 YES /___/ NO /X/

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 /X/

Investigation #2 YES /___/ NO /X/

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

_____

_____ 4/7/98

Signature Date

Title: Deputy Division Director

_____ _____

Signature of Division Director Date

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

NDA (20-869): COSOPT ™
(Dorzolamide Hydrochloride and Timolol Maleate)

Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Dorzolamide Hydrochloride & Timolol Maleate
2. Strengths	2.0%/0.5%
3. Trade Name	COSOPT ™
4. Dosage Form, Route of Administration	Sterile Ophthalmic Solution, Topical
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	20-869
7. Approval Date	
8. Exclusivity-Date First ANDA Could be Submitted	
Length of Exclusivity Period	
9. Applicable Patent Numbers and Expiration Dates:	U.S. Patent 4,797,413 Exp. Date: December12, 2004± and 4/27/2008(PTR)
	U.S. Patent 4,619,939* Exp. Date: October 28, 1993
	U.S. Patent 4,195,085 Exp. Date: March 25, 1997

±Patent Term Restoration (PTR) of U.S. Patent 4,797,413 has been applied for pursuant to 35 U.S.C. Section 156. When granted, the expiration date will be April 27, 2008.

*Licensed from the University of Florida.

March 17, 1997

Re: NDA 20-869 COSOPT ™
(Dorzolamide Hydrochloride and Timolol Maleate)
Information required in accordance with 21 U.S.C. Section 355(b)(1)

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, [21 U.S.C. 355(b)(1)], attached hereto please find patent information being submitted in support of the above-identified new drug application.

The undersigned declares that Patent Nos. 4,797,413, 4,619,939, 4,195,085, and 4,861,760 cover the compounds, formulation, composition, and/or method of treatment claims. This product is pending approval under Section 505 of the Federal Food, Drug and Cosmetic Act in the above-identified new drug application (NDA 20-869).

U.S. Patent No. 4,797,413 having an expiration date of December 12, 2004*, claims the chemical compound dorzolamide hydrochloride, the method of treating ocular hypertension, and a pharmaceutical formulation containing dorzolamide hydrochloride. U.S. Patent No. 4,619,939 having an expiration date of October 28, 2003 is owned by the University of Florida and licensed to Merck & Co., Inc., and claims a method of lowering intraocular pressure using a carbonic anhydrase inhibitor. U.S. Patent No. 4,195,085 having an expiration date of March 25, 1997, claims a method and a composition for treating glaucoma and for lowering intraocular pressure using timolol maleate in the presence of an ophthalmologically acceptable carrier.

A claim of infringement could be asserted if a person not licensed by the owner of the patents engaged in the manufacture, use, or sale of the above-noted drug product of this application for which approval is sought.

Patent Department

Merck & Co., Inc
P.O. Box 2000
Rahway NJ 07065-0907
Fax 908 594 4720
Tel 908 594 4000
Cable MERCKRAH
Telex 138825

September 18, 1997

MERCK

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 20-869 : COSOPT ™
(Dorzolamide Hydrochloride and Timolol Maleate)
Information required in accordance with 21 U.S.C. Section 355(b)(1)

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, [21 U.S.C. 355(b)(1)], attached hereto please find patent information supplementing that which was previously submitted in support of the above-identified new drug application.

The attached Item 13 has been amended to reflect the length of exclusivity period to be three years and to reflect that U.S Patent No. 4,797,413 will expire April 28, 2008, pursuant to 35 U.S.C. Section 156.

Sincerely,

Sylvia A. Ayler
Senior Attorney

Att. (Item 13 Statement)

NDA (20-869) : COSOPT ™
(Dorzolamide Hydrochloride and Timolol Maleate)

Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Dorzolamide Hydrochloride & Timolol Maleate
2. Strengths	2.0%/0.5%
3. Trade Name	COSOPT ™
4. Dosage Form, Route of Administration	Sterile Ophthalmic Solution, Topical
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	20-869
7. Approval Date	
8. Exclusivity-Date First ANDA Could be Submitted	
Length of Exclusivity Period	3 Years
9. Applicable Patent Numbers and Expiration Dates:	U.S. Patent 4,797,413 Exp. Date: April 28, 2008±
	U.S. Patent 4,619,939* Exp. Date: October 28, 1993
	U.S. Patent 4,195,085 Exp. Date: March 25, 1997

* Patent Term Restoration, pursuant to 35 U.S.C. Section 156, has been granted. The expiration date is April 28, 2008.

*Licensed from the University of Florida.

PEDIATRIC PAGE

(Complete for all original applications and an efficacy supplements)

NDA/ # **NDA 20-869** Applicant: **Merck Research Laboratories**
Supplement #
Therapeutic Class **4S**
Circle one: SE1 SE2 SE3 SE4 SE5 SE6
Action: (AP) AE NA
HFD-550
Trade (generic) name/dosage form: Cosopt (dorzolamide hydrochloride and timolol maleate) Sterile Ophthalmic Solution
Applicant Indication(s) previously approved: **N/A**
Pediatric labeling of approved indication(s) is adequate____ inadequate_____
Indication in this application: for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time.
(For supplements, answer the following questions in relation to the proposed indication.)

_____ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

_____ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

_____ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

_____ b. The applicant has committed to doing such studies as will be required.
____ (1) Studies are ongoing,
____ (2) Protocols were submitted and approved.
____ (3) Protocols were submitted and are under review.
____ (4) If no protocol has been submitted, explain the status on the back of this form.

____ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__X__ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain why pediatric studies are not needed.: The indication is not common in children.

____ 4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Ann Marie Jarska Project Manager April 1, 1998
Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Original **NDA 20-869**
HFD-550/DIV File
→NDA/PLA Action Package
HFD-510 G.Troendle (plus, for CDER APs and AEs, copy of action letter and labeling)
NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
5/95

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Corporate Blvd., Room N461,
Phone #: 827-2391

From: Division of Anti-inflammatory, Analgesic (HFD - 550)
Attention: Bart Ho Phone: 827-2502 Date: December 12, 1997

Subject: Request for Assessment of a Trademark for a Proposed Drug Product
NDA#: 20-869, Dorzolamide Hydrochloride and Timolol Maleate
Trademark: COSOPT
Proposed alternate: None
Company Name: Merck & Co. Inc., BLA-30, West Point PA 19486
Established name, including dosage form:

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution.

Other trademarks by the same firm for companion products:

TRUSOPT (Dorzolamide Hydrochloride Ophthalmic Solutions
TIMOPTIC (Timolol Maleate Ophthalmic Solutions)

Indications for Use (may be a summary if proposed statement is lengthy): Ophthalmic

Initial comments from the submitter (concerns, observations, etc.): None

Review Chemist's Comment: None

APPEARS THIS WAY
ON ORIGINAL

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

June 25, 1997

MERCK
Research Laboratories

Wiley Chambers, M.D. - Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products
HFD-550 Room 9B-23
Office of Drug Evaluation V (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Chambers:

Original New Drug Application

NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution)

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL) is submitting a New Drug Application (NDA) for COSOPT™ (dorzolamide hydrochloride/timolol maleate ophthalmic solution), NDA 20-869.

COSOPT™ is a combination of timolol, a non-selective adrenergic receptor blocking agent which, when applied topically to the eye, reduces elevated as well as normal intraocular pressure (IOP), and dorzolamide, a potent topical inhibitor of carbonic anhydrase isoenzyme-II (CA_{II}), which decreases aqueous humor secretion resulting in a reduction of IOP. In this application COSOPT™ is also referred to as MK-0507A, 2.0% dorzolamide hydrochloride/0.5% timolol maleate combination, dorzolamide hydrochloride/timolol maleate, dorzolamide/timolol and MK-507/timolol.

This application supports an indication for COSOPT™ for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma when concomitant therapy is appropriate.

Eight clinical trials are provided in this application. Two clinical pharmacology studies demonstrated the initial safety and tolerability and the appropriate dose selection for COSOPT™. In Phase III, two studies examined the equivalence of COSOPT™ twice daily to concomitant administration of 2.0% dorzolamide hydrochloride and 0.5% timolol maleate. The other four

We consider the filing of this New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Edwin Hemwall, Ph.D. (610/397-2306).

Sincerely yours,

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments
Q:\CARROLL\WMA\COSOPT\INPROC\COSCL

Federal Express No. 1

Desk Copy: (Item 3)

Philadelphia District Office, Attn: Ms. Debra L. Pagano, Food and Drug Administration Room 900, U.S. Custom House, 2nd & Chestnut Streets
Philadelphia, PA 19106-2973
Federal Express No. 2

Desk copy: (Letter and Patent Information Only)

Mr. George Scott, HFD-084, 5516 Nicholson Lane, Rm. 238, Rockville, MD 20857
Hand Delivered

ORIGINAL

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

July 1, 1997

MERCK
Research Laboratories

Ms. Joanne Holmes
Food and Drug Administration
9201 Corporate Blvd., HFD-550
Rockville, Maryland 20850

NEW CORRESPONDENCE

NDA 20-869: COSOPT™ Ophthalmic Solution
(Dorzolamide Hydrochloride/Timolol Maleate)

Dear Ms. Holmes:

Reference is made to the Original New Drug Application NDA 20-869 for COSOPT™ Ophthalmic Solution submitted on June 25, 1997 and to the June 26, 1997 telephone conversation between Ms. Lori Gorski and Ms. Joanne Holmes (FDA) and Dr. William Roberts (MRL). In that telephone conversation, a desk copy of the COSOPT™ carton and label text was requested.

Attached with this submission is the COSOPT™ carton and label text included in Item 4 of the NDA.

Please note that the Computer Assisted New Drug Application (CANDA) will also include the COSOPT™ carton and label text in Item 4.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Edwin Hemwall, Ph.D. (610/397-2306).

Sincerely yours,

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachment
Q:\CARROLL\DRAFTS\FDAREQ.DOC

Federal Express #1

FILING COMPLETE

LETTER DATED

DOCUMENTS

William G. Roberts, M.D.
Director
Regulatory Affairs

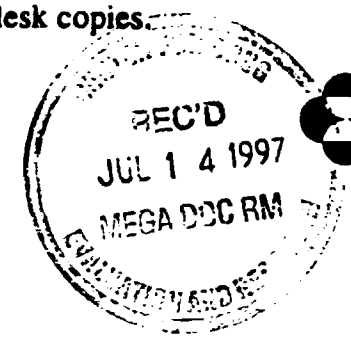
Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

NC

NDA 20-869 CORRESP.

July 9, 1997

These copies are
OFFICIAL FDA Copies
not desk copies.



MERCK
Research Laboratories

Wiley Chambers, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products - HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Chambers:

NDA 20-869: COSOPT™ Ophthalmic Solution

Response to FDA Request

Reference is made to the Original New Drug Application 20-869 for COSOPT™ Ophthalmic Solution submitted on June 25, 1997 and to the telephone conversation on July 1, 1997 between Ms. Joanne Holmes (FDA) and Dr. William Roberts (MRL) regarding the FDA Form 356H contained in the original application.

Per Ms. Holmes request, attached are 6 copies of the FDA Form 356H including references to for COSOPT™ Ophthalmic Solution, NDA 20-408 TRUSOPT™ Ophthalmic Solution and NDA 18-086 TIMOPTIC™ Ophthalmic Solution.

Questions concerning this supplemental application should be directed to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

William G. Roberts

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments
Q:\CARROLL\DRAFTS\356REQ.DOC

Certified No. P 963 213 508

1 Desk Copy: Ms. Joanne Holmes, HFD-550
Certified No. P 963 213 507

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

DESK COPY

July 9, 1997

Dr. Wiley Chambers, M.D., Acting Director
Division of Anti-Inflammatory, Analgesics and
Ophthalmic Drug Products, ODE V, HFD 550
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 20-869: COSOPT™ Ophthalmic Solution
(Dorzolamide Hydrochloride/Timolol Maleate)

Dear Dr. Chambers:

Reference is made to the Original New Drug Application NDA 20-869 for COSOPT™ Ophthalmic Solution submitted on June 25, 1997 and to telephone conversations on June 30 and July 1, 1997 between Ms. Joanne Holmes (FDA) and Dr. William Roberts (MRL). In that telephone conversation, Ms. Holmes requested that pertinent information be provided to the microbiology reviewer.

Attachment I is a summary list of data contained in the Chemical and Pharmaceutical Manufacturing and Control Documentation section of the Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution NDA pertaining to sterility and microbiology issues. Attachment II contains the respective pages from the NDA.

In addition, Volume 1.1 containing Item 1 (the overall Index to Contents of Application) and Volume 1.2, containing Item 2 (Synopsis of Application), which is the overall summary are provided for your review.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

William G. Roberts

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachment
Q:\CARROLL\DRAFTS\MICROREV.DOC

Federal Express #1

Desk Copy: Ms. Joanne Holmes, HFD-550
Federal Express #2

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

These copies are OFFICIAL FDA Copies
not desk copies.

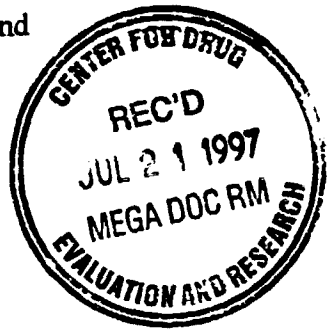
DUPLICATE

July 21, 1997

NEW CORRESP

MERCK
Research Laboratories

Wiley Chambers, M.D. - Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products
HFD-550 Room 9B-23
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850



Dear Dr. Chambers:

NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution)

FDA Request for Additional Copies

Reference is made to the above cited New Drug Application NDA 20-869 for COSOPT™ (dorzolamide hydrochloride/timolol maleate ophthalmic solution) submitted on June 25, 1997 and to a telephone conversation between Dr. Wiley Chambers and Ms. Joanne Holmes (FDA) and Dr. William Roberts (MRL) on July 18, 1997. In that telephone conversation Ms. Holmes requested that we provide an additional hard (paper) copy of Item 11: Case Report Tabulations for Dr. Chambers use during the review.

As requested, attached with this letter is an additional copy of Item 11, Volumes 1.29 through 1.60.

We consider the filing to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

William G. Roberts

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments
Q/CARROLL/WMA/COSOPT/COSREQ

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

August 1, 1997

MERCK
Research Laboratories

Michael Weintraub, M.D. - Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products, (CDER)
Office of Drug Evaluation V, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NEW CORRESP

NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution)

Response to FDA Request

Dear Dr. Weintraub:

Reference is made to the above cited NDA and to a telephone conversation between Dr. Bart Ho (FDA) and Dr. William Roberts (MRL) on July 14, 1997 in which Dr. Ho requested the Establishment Registration Number (CFN) for the Barceloneta site and the Labeler Code Number for the LaVallee site. Additional reference is made to a facsimile sent the same day to Dr. Ho from Dr. Roberts containing the requested information.

Attached for the Official NDA files is a copy of the facsimile sent on July 14, 1997.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachment

Certified No. P 963 213 488
Q/YAR/LAC/LTR/ESTAB

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

August 21, 1997

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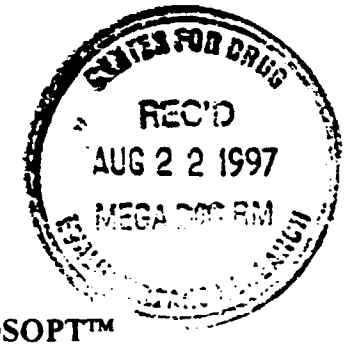
MERCK
Research Laboratories

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesics, and
Ophthalmic Drug Products, HFD-550,
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution)

Amendment to the New Drug Application

Dear Dr. Weintraub:

Reference is made to the New Drug Application for COSOPT™ submitted on June 25, 1997. An inadvertent error was noted in Item 3: Chemistry and Pharmaceutical Manufacturing and Control Documentation I. Summary C. Drug Product Information. The information provided only included target fill for the 5 mL label claim. However, COSOPT™ will be supplied in the 2.5 mL (physician sample) and the 10 mL label claim.

With this letter, we are amending this application to include the target fill for these container fills. Attached is the revised page (Page C-13). We apologize for the inconvenience.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts, M.D.
Director, Regulatory Affairs

Q:CAT LAC LETTERS\20869

Attachment

Federal Express No.

William G. Roberts, M.D.
Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

September 5, 1997

Dr. Tony Carreras
Division of Scientific Investigations
FDA Office of Compliance
7529 Standish Place
Rockville, MD 20855

MERCK
Research Laboratories

NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution)

Dear Dr. Carreras:

Reference is made to the above cited NDA submitted on June 25, 1997 and to a telephone conversation on August 14, 1997 between Dr. Tony Carreras, Medical Officer (FDA) and Dr. William Roberts (MRL). In that telephone conversation Dr. Carreras requested information for three clinical investigator sites, which FDA plans to inspect as part of the COSOPT™ NDA review.

Attached is the following information for sites 047-003 (Dr. Brian Bowe), 063-023 (Dr. Robert Williams) and 064-021 (Dr. Thomas Walters):

- Study Protocol/amendment under which study was conducted
- Data listing on Primary Endpoint - Intraocular Pressure (IOP)
- Clinical Adverse Experiences (AEs) listings in specific terms for all patents at each site

Please note that no laboratory AEs or "Other AEs" occurred. Therefore only clinical AEs are included in the AE listing.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments
Q:\CARROLL\DRAFTS\FDAINSP.DOC

Desk Copy: NDA 20-869: COSOPT™ Official Regulatory Files

Federal Express #1

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

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BH

OMG AMENDMENT

DUPLICATE

September 19, 1997

MERCK
Research Laboratories

Michael Weintraub, M.D. - Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products
HFD-550 Room 9B-23
Office of Drug Evaluation V (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-869: COSOPT™ Ophthalmic Solution
(Dorzolamide Hydrochloride)

Amendment to the New Drug Application

Dear Dr. Weintraub:

Reference is made to the New Drug Application for COSOPT™ Ophthalmic Solution submitted on June 25, 1997. Reference is also made to a telephone conversation between Ms. Joanne Holmes (FDA) and Dr. William Roberts (MRL) on September 16, 1997 regarding the exclusivity period of U.S. Patent No. 4,797,413.

As requested, attached with this letter, Merck provides an update to Item 13: Patent Information and Item 14: Patent Certification to reflect the length of exclusivity period.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

for

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachment
Q:/CARROLL/DRAFTS/PATCOS

Federal Express

William G. Roberts, M.D.
Director
Regulatory Affairs

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Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

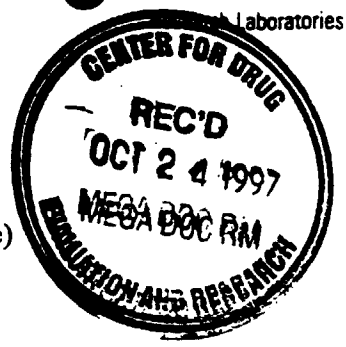
October 23, 1997

541

ORIG AMEND

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
CDER, ODE V HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

MERCK Laboratories



NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride and Timolol Maleate)

Safety Update Report

Dear Dr. Weintraub:

Reference is made to the Original New Drug Application (NDA) for COSOPT™ (dorzolamide hydrochloride and timolol maleate) submitted on June 25, 1997 for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

With this letter, Merck Research Laboratories (MRL) is submitting the Safety Update Report (SUR) to NDA 20-869. This report provides updated or corrected safety information for dorzolamide hydrochloride and timolol maleate received subsequent to the original NDA. As of the date of this submission, two additional studies involving COSOPT™ are ongoing, but neither has been completed. Therefore, this brief SUR consists of serious adverse experiences reported between the MRL Worldwide Adverse Experience System (WAES) cutoff date for the Original Application (February 3, 1997) and the WAES cutoff date established for this Safety Update Report (June 30,1997). Only one serious AE was reported during this time.

We consider the filing of this information to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments
Q/YAR/LAC/LTR/COSSUR

Federal Express #1

William G. Roberts, M.D.
Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

December 19, 1997

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products - HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

Dear Dr. Weintraub:

NDA 20-869: COSOPT® Ophthalmic Solution
(Dorzolamide Hydrochloride and Timolol Maleate)

FDA Request for Information

Reference is made to the New Drug Application cited above submitted on June 25, 1997 and to a November 1, 1996 facsimile from Dr. Eric Sheinin (FDA) to Dr. Bonnie Goldmann (MRL) regarding stability data from the manufacturing site. In that communication the Agency requested that we submit three months accelerated and real time data from one batch of COSOPT® manufactured at the West Point, PA facility.

As requested, attached please find the six month stability data for dorzolamide hydrochloride and timolol maleate opthalmic solution, Lot Number Rx 1000385/0500607. This lot was manufacutred at West Point, PA, the site of manufacture proposed for the marketed product.

We consider the filing of this information to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts, M.D.
Director, Regulatory Affairs

Attachment

Federal Express #1
Q/YAR/LAC/LTR/6MOCOS

(2) Desk copies/att: [redacted] Lobianco, HFD-550
Federal Express #2

William G. Roberts, M.D.
Director
Regulatory Affairs

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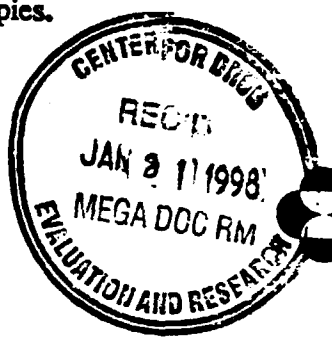
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

NC
NEW CORRESP

DUPLICATE



MERCK
Research Laboratories

January 20, 1998

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Weintraub:

NDA 20-869: COSOPT Ophthalmic Solution

General Correspondence

Reference is made to the pending New Drug Application cited above submitted on June 25, 1997 and to the July 22, 1997 request by Merck Research Laboratories (MRL) for a waiver of the requirement to submit Item 12: Case Report Forms (CRF) in hard copy. The Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products has previously indicated at the Pre-NDA meeting on October 21, 1997 their willingness to accept the CRFs in electronic form only. Reference is also made to the Federal Register Rule, public docket 92N-0251, regarding electronic records and signatures, published on March 20, 1997 with an effective date of August 20, 1997.

Now that the rule has become effective, we wish to again request an official waiver of the requirement to provide the CRFs in hard copy. As stated in the July 22, 1997 communication, the electronic CRFs have been prepared in a manner that is substantially consistent with the Rule and copies of the CRFs will be maintained at Merck as required under 21 CFR 312.57 (b).

Questions and concerns should be directed to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

William G. Roberts, M.D.
Director, Regulatory Affairs

q:\carroll\memos\12waiver.doc

Federal Express #1

Desk Copy to Ms. Lori Gorski - HFD-550, Federal Express #1

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486
Fax 610 397 2516
Tel 610 397 7052

February 12, 1998

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
CDER, ODE V HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

MERCK
Research Laboratories

NDA 20-869: COSOPT™
(Dorzolamide Hydrochloride and Timolol Maleate)

Response to FDA Request

Dear Dr. Weintraub:

Reference is made to the Original New Drug Application (NDA) for COSOPT™ (dorzolamide hydrochloride and timolol maleate) submitted on June 25, 1997. Referenee is also made to the February 11, 1998 telephone conversation between Ms. Lori Gorski (FDA) and Dr. William Roberts (MRL) requesting we provide a diskette containing the labeling revisions, as submitted by MRL in a January 8, 1998 facsimile communication.

Attached with this letter, we are providing the requested information as follows:

- Hard copy of annotated circular, illustrating revisions
- Hard copy of clean running text, incorporating those revisions
- Diskette containing the annotated circular and clean running text

We consider the filing of this information to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments
Q/YAR/LAC/LTR/COSLAB

Federal Express #1

Desk Copy w/ Diskette: Dr. Wiley Chambers HFD-550 Federal Express #1
Ms. Lori Gorski HFD-550 Federal Express #1

William G. Roberts, M.D.
Director
Regulatory Affairs

DECK COPY

Merck & Co., Inc
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

March 2, 1998

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
CDER, ODE V HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

MERCK
Research Laboratories

Dear Dr. Weintraub:

NDA 20-869: COSOPT™ Ophthalmic Solution

Response to FDA Request for Information

Reference is made to the NDA cited above submitted on June 25, 1997 and to the February 11, 1998 facsimile communication from Ms. Lori Gorski (FDA) to Dr. William G. Roberts (MRL) providing Agency comments regarding the COSOPT™ NDA. Reference is also made to a teleconference of February 25, 1998 between Dr. Wiley Chambers and Ms. Lori Gorski (FDA) and MRL representatives and to the February 25, 1998 submission providing responses to questions 2 through 12 of the Agency's comments in the February 11, 1998 facsimile.

With this submission, we are providing the response to question 1, which requested revised labeling. The revisions noted in the Adverse Reactions section reflect the proposals and discussion during our teleconference. Attached are the following:

- Draft annotated package circular illustrating the revisions
- Clean running text, incorporating those revisions
- A diskette in Word 6.0 version of the draft annotated package circular and clean running text

We consider the filing of this supplement to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts

William G. Roberts, M. D.
Director
Regulatory Affairs

Attachments
Q\CARROLL\DRAFTS\211pc.doc

Federal Express #1
2 Desk copies w/diskette: Ms. Lori Gorski, HFD-550, Federal Express #1

William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

March 16, 1998

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products - HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

MERCK
Research Laboratories

Dear Dr. Weintraub:

NDA 20-869: COSOPT™ Ophthalmic Solution
(Dorzolamide Hydrochloride/Timolol Maleate)

Amendment to New Drug Application

Reference is made to the New Drug Application for COSOPT™ Ophthalmic Solution submitted on June 25, 1997 and to several telephone conversations between Drs. Roberts and/or Goldmann (MRL) and Dr. Chambers (FDA) from March 5 through March 9, 1998. Reference is also made to the March 5, 1998 facsimile communication from Dr. Chambers to Dr. Roberts and to the telephone conversation on March 13, 1998 between Ms. Lori Gorski (FDA) and Dr. William Roberts (MRL).

With this submission, Merck is providing responses to questions raised by the Agency and agreements reached during the above mentioned telephone conversations. All agreed upon changes have been incorporated in the attachments to this letter. Attached are the following:

- Draft annotated mock-up, illustrating revisions
- Clean running text, incorporating revisions

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts, M.D.
Director, Regulatory Affairs

Attachments
q:\carroll\drafts\cosdft.doc

2 Desk Copies w/diskette (MSWord Version 6.0): Ms. Lori Gorski

Federal Express

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-869

JUL 11 1997

Merck Research Laboratories
Attention: William G. Roberts, M.D.
Vice President, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, Pennsylvania 19486-0004

Dear Dr. Roberts:

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

Name of Drug Product: Cosopt (dorzolamide hydrochloride/timolol maleate) Sterile Ophthalmic Solution

Therapeutic Classification: Standard

Date of Application: June 25, 1997

Date of Receipt: June 26, 1997

Our Reference Number: NDA 20-869

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 25, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Lori Gorski, Project Manager, at (301) 827-2090.

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

Sincerely,

Lissante LoBianco
Acting Supervisory Project Manager
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research