CENTER FOR DRUG EVALUATION AND RESEARCH

75-412

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-411 (0.25% base)
75-412 (0.5% base)

Date of Submission:
April 14, 2000 (Amendment)

Applicant's Name: Novex Pharma

Established Name: Timolol Maleate Ophthalmic Solution, USP

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (10 mL and 15 mL) – Satisfactory as of April 14, 2000 submission

Carton Labeling: (10 mL and 15 mL) – Satisfactory as of ~~April 14, 2000~~ March 16, 2000 submission

Professional Package Insert Labeling: Satisfactory as of March 16, 2000 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Timoptic

NDA Number: 18-086

NDA Drug Name: Timolol Maleate Ophthalmic Solution

NDA Firm: Merck & Co., Inc.

Date of Approval of NDA Insert and supplement #052: March 18, 1998

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison

Basis of Approval for the Carton Labeling: Side-by-side comparison

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based on the reference listed drug, (Timoptic™ - Merck & Co., Inc.; approved March 18,1998).

2. Packaging
The RLD packages its product in white, opaque, plastic ophthalmic dispensers with controlled drop tips in 2.5 mL, 5 mL, 10 mL, and 15 mL. The 0.25% product has blue caps. The 0.5% product has yellow caps.

The applicant proposes to package its products in 10 mL and 15 mL white, opaque bottles with white, opaque ophthalmic caps with sealing tape. The opacity of the bottles should adequately protect the product from light.

3. Labeling
Firm re-submitted container labels because included a 200% depiction on the same page as the printer's proof which was not FOIable.

4. Inactive Ingredients
There does not appear to be a discrepancy in the listing of inactives between the DESCRIPTION section of the insert labeling and the Components and Composition Statements.

5. USP Issues
USP - Preserve in tight, light-resistant containers.
RLD - Store at RT, 15-30°C (59-86°F). Protect from freezing. Protect from light.
ANDA - same as RLD.

6. Bioequivalence Issues - Waiver granted 10/19/98.

7. Microbiology Issues - pending

8. Patent/Exclusivity Issues - None pending

Date of Review:
April 19, 2000

Date of Submission:
April 14, 2000 (Amendment)

Primary Reviewer:

Date:
4/19/00

Secondary Reviewer:

Date:

Team Leader:

Date:
4/20/2000

cc:

Timolol Maleate Ophthalmic Solution, USP
0.50%
ANDA #75-412
Reviewer: Mamata S. Gokhale
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Apotex Corp.,
U.S. Agent for: **Novex Pharma**
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061
Submission Date: July 02, 1998

Addendum to the Review of a Waiver Request

Objective:

The purpose of this review is to delete an incorrect footnote in the formulation comparison.

Background

1) The firm submitted a request for the waiver of in vivo bioavailability/bioequivalance study requirements based on 21 CFR 320.22(b)(1) for its proposed product Timolol Maleate Ophthalmic Solution, USP, 0.50% (submission dated 6/2/98). The reference listed drug is Timoptic® Sterile Ophthalmic Solution, USP, supplied as 0.50%, manufactured by Merck & Co., Inc.

2) The DBE found the submission acceptable and granted a waiver to Apotex/Novex Pharma's Timolol Maleate Ophthalmic Solution, USP, 0.50%. See the DBE review finalized on 10/19/98.

3) In the DBE review of 10/19/98, the incorrect footnote #3 was "the test product uses solution per ml of test product (page 88 of the ANDA) which amounts to as claimed; however, this amount is within approved safety limits (FDA/CDER inactive ingredient guide, 1996, page 8)".

4) In this addendum, the incorrect footnote #3 is deleted.

Formulation Comparison

Ingredient (% w/v)	Reference listed product	Test product
[1]Timolol Maleate,	0.50	0.50
[2]Total Phosphates,		
Benzalkonium Chloride		
Sodium Hydroxide,		

Comments

1) This addendum supercedes the DBE review of 10/19/98.

2) The DBE recommendations remain the same as in the review of 10/19/98.

Recommendations

The Division of Bioequivalence agrees that the information submitted by Apotex Corp., for Novex Pharma demonstrates that Timolol Maleate Ophthalmic Solution, USP, 0.50%, falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of an *in vivo* bioequivalence study requirement for Timolol Maleate Ophthalmic Solution, USP, 0.50%, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Timoptic® Sterile Ophthalmic Solution, USP, also 0.50%, manufactured by Merck & Co., Inc.

Mamata S. Gokhale, Ph.D. mamata Gokhale 9/7/00
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT
for FT INITIALED BDAVIT Mohsen H. Makary Date 9/7/00

Concur: Barbara M Davit Date 9/7/00
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc:

Timolol Maleate Ophthalmic Solution, USP
0.50%
ANDA #75-412
Reviewer: Mamata S. Gokhale
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Apotex Corp.,
U.S. Agent for: **Novex Pharma**
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061
Submission Date: July 02, 1998

Review of a Waiver Request

Background

1) The firm has submitted a request for a waiver of in vivo bioavailability/bioequivalance study requirements based on 21 CFR 320.22(b)(1) for its proposed product Timolol Maleate Ophthalmic Solution, USP, 0.50%. The reference listed drug is Timoptic® Sterile Ophthalmic Solution, USP, supplied as 0.50%, manufactured by Merck & Co., Inc.
2) Timoptic® Sterile Ophthalmic Solution, USP, is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma and also in the event of inadequate response to multiple antiglaucoma therapy.
3) The reference product, Timoptic® Sterile Ophthalmic Solution, USP, is to be applied topically in the eye. The test product, Timolol Maleate Ophthalmic Solution, USP, 0.50%, is proposed to be administered by similar route.

Formulation Comparison

Ingredient (% w/v)	Reference listed product	Test product
[1]Timolol Maleate	0.50	0.50
[2]Total Phosphates,		
[3]Benzalkonium Chloride,		
[4]Sodium Hydroxide,		

Comments

1) The proposed product is an ophthalmic solution intended for topical application in the eye.
2) The active ingredient, route of administration, dosage form and strength of the test product are same as those of the reference listed product.
3) All ingredients in test and reference products are qualitatively the same.

Recommendations

The Division of Bioequivalence agrees that the information submitted by Apotex Corp., for Novex Pharma demonstrates that Timolol Maleate Ophthalmic Solution, USP, 0.50%, falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of an *in vivo* bioequivalence study requirement for Timolol Maleate Ophthalmic Solution, USP, 0.50%, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Timoptic® Sterile Ophthalmic Solution, USP, also 0.50%, manufactured by Merck & Co., Inc.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 10/9/98
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT BDA 10/8/98
FT INITIALED BDAVIT Barbara M Davit Date 10/3/98

Concur: Dale P. Conner Date 10/20/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: