# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75411**

# BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS

# DIVISION OF BIOEQUIVALENCE

ANDA # 75-411 SPONSOR: Apotex Corp, for Novex Pharma.
DRUG AND DOSAGE FORM: Timolol Maleate Ophthalmic Solution, USP
Strength(s): 0.25%
Type of Study: SD SDF MULT OTHER
X

STUDY SITE: N/A
STUDY SUMMARY: N/A
FORMULATION: Acceptable
Waiver is granted.

PRIMARY REVIEWER: Mamata S. Gokhale, Ph.D. BRANCH: III
INITIAL MSK DATE 10/9/98

TEAM LEADER: Barbara M. Davit, Ph.D. BRANCH: III
INITIAL BMD Date 10/9/98

DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL DPC DATE 10/19/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL DPC DATE 10/19/98

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-411 APPLICANT: Apotex Corp., for Novex Pharma
DRUG PRODUCT: Timolol Maleate Ophthalmic Solution, USP 0.25%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**Timolol Maleate Ophthalmic Solution, USP**
0.25%
ANDA #75-411
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, 0.25%. The reference listed drug is Timoptic® Sterile Ophthalmic Solution, USP, supplied as 0.25%, 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, 0.25%, is proposed to be administered by similar route.

### Formulation Comparison

| Ingredient (% w/v) | Reference listed product | Test product |
|---|---|---|
| [1]Timolol Maleate, USP | 0.25 | |
| [2]Total Phospates, USP | | |
| [3]Benzalkonium Chloride, NF | 0.01 | |
| [4]Sodium Hydroxide, NF | to adjust pH | to adjust to pH |
| Water for Injection USP (reference) or Purified Water, USP (test) | q.s. to batch size | q.s. to batch size |

[1]Active ingredient, [2]Sodium Phospate Dibasic and Sodium Phospate Monobasic (both anhydrous) combined, [3]Test product uses mg of 50% w/v solution per ml of test product (pg 88 of the ANDA) which amounts to 0.02%w/v and not 0.01% w/v as claimed; however, this amount is within approved safety limits (FDA/CDER inactive ingredient guide, 1996, pg 8).

See addendum to waiver request enclosed 8/1/00

**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, 0.25%, 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, 0.25%, 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 0.25%, manufactured by Merck & Co., Inc.

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

RD INITIALED BDAVIT /S/ 10/9/98
FT INITIALED BDAVIT /S/ Date 10/9/98

Concur: /S/ Date 10/19/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA# 75-411 (original, duplicate), Gokhale, HFD-658, Drug File, Division File

**Timolol Maleate Ophthalmic Solution, USP**
0.25%
ANDA #75-411
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, 0.25% (submission dated 6/2/98). The reference listed drug is Timoptic® Sterile Ophthalmic Solution, USP, supplied as 0.25%, 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, 0.25%. 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 mg of 50% w/v solution per ml of test product (page 88 of the ANDA) which amounts to 0.02% w/v and not 0.01% w/v 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, USP | 0.25 | |
| [2]Total Phosphates, USP | | |
| Benzalkonium Chloride, NF | 0.01 | |
| Sodium Hydroxide, NF | to adjust pH | to adjust to pH |
| Water for Injection USP (reference) or Purified Water, USP (test) | q.s. to batch size | q.s. to batch size |

[1]Active ingredient, [2]Sodium Phosphate Dibasic and Sodium Phosphate Monobasic (both anhydrous) combined.

**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, 0.25%, 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, 0.25%, 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 0.25%, manufactured by Merck & Co., Inc.

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

RD INITIALED BDAVIT
for FT INITIALED BDAVIT /S/ Date 9/7/00

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

cc: ANDA# 75-411 (original, duplicate), Gokhale, HFD-658, Drug File, Division File