CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75411

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY FOR 75-411

ANDA: 75-411

FIRM: Novex Pharma

DRUG: Timolol Maleate

Dosage: Sterile Ophthalmic Solution

STRENGTH: 0.25%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 6/11/99

BIO STUDY/BIOEQUIVALENCE STATUS: Bio waiver was granted 10/19/98

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has provided 12 weeks satisfactory accelerated stability data at %RH. For both sizes and 9months for 10 mL and 18 months for 15 mL stability data at %RH.

LABELING REVIEW STATUS: Labeling is satisfactory 4/20/00

STERILIZATION VALIDATION: Microbiology is satisfactory 5/15/00

BATCH SIZE: The firm has submitted the master formula and manufacturing instructions for intended production batch liters. Also provided copies of the executed batches 7x35 and 6x56 for liters each. The firm will be using the same drug substance manufacture, same procedure and same equipment.

COMMENTS: The application is Approvable.

Reviewer: Nashed E. Nashed, Ph.D. Date: 8/16/00

Supervisor: Paul Schwartz, Ph.D. P S 8/21/00

1. CHEMISTRY REVIEW NO 4

2. ANDA # 75-411

3. NAME AND ADDRESS OF APPLICANT

Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

4. LEGAL BASIS FOR SUBMISSION

In the firm opinion and the best of their knowledge there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug and Timoptic is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)

Original 7/6/98

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Timolol Maleate, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 3/15/00 – Microbiology
Amendment 3/31/00 – Labeling
Amendment 4/14/00 - Labeling
Amendment 8/4/00

10. PHARMACOLOGICAL CATEGORY

Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF

13. DOSAGE FORM

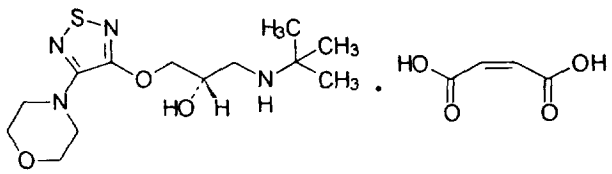
Sterile Ophthalmic Solution

14. POTENCY

0.25%

15. CHEMICAL NAME AND STRUCTURE

Timolol Maleate. 2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (*S*)-, (*Z*)-2-butendioate (1:1) (salt). $C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$. Mwt. 432.5. 26921-17-5. Anti-adrenergic (Beta-receptor). USP 23, page 1553.



16. RECORDS AND REPORTS

17. COMMENTS

The microbiology is satisfactory 5/15/00

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 8/16/00

Supervisor: Paul Schwartz, Ph.D. PS 8/16/00

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secret and/or

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ry Comments to be Provided to the Applicant.

1-1 75-411 APPLICANT: Novex Pharma

PRODUCT: Timolol Maleate Ophthalmic Solution USP, 0.25%

deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Please revise your drug substance specifications regarding organic volatile impurities according to USP 24.

2. DMF is deficient. The DMF holder has been notified. Please do not respond to this amendment until you have been notified by the DMF holder that the DMF deficiencies have been addressed.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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1./ nistry Comments to be Provided to the Applicant.

A: 75-411 APPLICANT: Novex Pharma

ug PRODUCT: Timolol Maleate Ophthalmic Solution USP, 0.25%

e deficiencies presented below represent MAJOR deficiencies.

. Deficiencies:

1. Please revise your drug substance specifications to include limits for the total unknown impurities.

2. Please provide the specific rotation results on the USP reference standard using the British Pharmacopeial method.

3. Please revise your in-process test to include acceptance limits for density of the drug product.

4. Please explain what you mean by report for information only for benzalkonium chloride assay and for Timolol assay on p. 697.

5. Please provide a color test (e.g., AphA) for the finished drug product.

6. Please revise your specifications for the finished drug product to include test, procedure and acceptance limits for impurities and degradation products.

7. Please revise your stability specifications to include a quantitative color test and osmolality.

8. Please revise your stability specifications to provide acceptance limits for seal integrity and adhesive material migration.

9. Please revise your stability specifications to include limits for total unknown and known degradation products.

10. Please provide certification that no other OVI's are used in the synthesis of the drug substance.

11. Please provide a description for the cycling stability study.

12. DMF is deficient. The DMF holder has been notified.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application regarding the manufacturing and testing the drug product should be in compliance with CGMP at the time of the approval.

2. USP methods are the regulatory methods and will prevail in the event of dispute.

3. Your microbiological section is under review.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research