

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-330 / S-017

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. ORGANIZATION HFD-550	2. NDA Number(s) 20-330
3. Name and Address of Applicant (City & State): Merck & Co., Inc. Sumneytown Pike, P.O. Box 4, BLA-20 West Point, PA 19486 (Virginia Snyder at telephone 484-344-7984)		4. AF No. 5. Supplement(s) Number(s) Date(s) SLR017 20-June-2003
6. Drug Name: TIMOPTIC-XE™	7. Nonproprietary Name: Timolol Maleate Ophthalmic Gel Forming Solution	8. Amendments & Other (reports, etc.) - Dates Annual Report
9. Supplement Provides For: the addition of pH and osmolarity to the label in the DESCRIPTION section and a full description of containers and fill size in the HOW TO SUPPLY section.		
10. Pharmacological Category: β ₁ and β ₂ adrenergic receptor blocking agent used to reduce intraocular pressure	11. How Dispensed: <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Sterile Ophthalmic Gellan Solution	Potency(ies): Dorzolamide HCl 2.0% Timolol Maleate 0.5%	
15. Chemical Name and Structure: (-)-1-tert-butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-y)oxy]-2-pranol maleate (1:1) salt		16. Records/Reports Current: <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No Reviewed: <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No
17. Comments: In response to the request by Lisa Hubbard on 01/04/02 telephone conversation applicant provides for changes in the Labeling Section of the approved NDA for TIMOPTIC-XE™, the changes include the addition of pH and osmolarity to the label in the DESCRIPTION section and descriptive information of the product container and fill size in the HOW SUPPLY section. This is acceptable. However, "color coded polypropylene cap" was referred to medical officer for clarification.		
18. Conclusions and Recommendations: From CMC viewpoint and based on the information submitted this supplement is recommended for approval. CC: Original NDA 20-330 HFD-550/Division File HFD-550/Med/Wchambers HFD-550/LNg HFD-550/CSO/MPuglisi HFD-830/CwChen HFD-550/YLu R/D initialed by : Linda Ng		
19. REVIEWER		
Name:	Signature:	Date Completed:

REVIEW NOTES

DESCRIPTION: (The additional sentence is noted by bold font)

Currently used:

TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths. Each mL of TIMOPTIC-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TIMOPTIC-XE 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: GELRITE* gellan gum, tromethamine, mannitol, and water for injection. Preservative: benzododecinium bromide 0.012%.

Proposed:

TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths. **The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm.** Each mL of TIMOPTIC-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TIMOPTIC-XE 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: GELRITE* gellan gum, tromethamine, mannitol, and water for injection. Preservative: benzododecinium bromide 0.012%.

HOW SUPPLIED (Changed as noted in bold font)

Currently used:

TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution is a colorless to nearly colorless, slightly opalescent, and slightly viscous solution.

No. 3557 — TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution, 0.25% timolol equivalent, is supplied in OCUMETER*, a white, opaque, plastic, ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3557-32, 2.5 mL

NDC 0006-3557-03, 5 mL.

No. 3558 — TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution, 0.5% timolol equivalent, is supplied in OCUMETER, a white, opaque, plastic, ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3558-32, 2.5 mL

NDC 0006-3558-03, 5 mL.

Storage

Store between 15° and 25°C (59° and 77°F). AVOID FREEZING. Protect from light.

Proposed:

TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution is a colorless to nearly colorless, slightly opalescent, and slightly viscous solution.

No. 3557 — TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution, 0.25% timolol equivalent, is supplied in OCUMETER[®], a white, opaque, LDPE, plastic, ophthalmic dispenser with a controlled drop tip and **color coded polypropylene cap** as follows:

NDC 0006-3557-32, 2.5 mL in a 5 mL bottle

NDC 0006-3557-03, 5 mL in a 7.5 mL bottle

No. 3558 — TIMOPTIC-XE Sterile Ophthalmic Gel Forming Solution, 0.5% timolol equivalent, is supplied in OCUMETER, a white, opaque, LDPE, plastic, ophthalmic dispenser with a controlled drop tip and **color coded polypropylene cap** as follows:

NDC 0006-3558-32, 2.5 mL in a 5 mL bottle

NDC 0006-3558-03, 5 mL in a 7.5 mL bottle

Storage

Store between 15° and 25°C (59° and 77°F). **AVOID FREEZING.** Protect from light.

Comment:

It is not clear what does “**color coded polypropylene cap**” means. This issue was referred to medical officer’s attention.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Yong-De Lu
12/8/03 04:27:54 PM
CHEMIST

Linda Ng
12/10/03 03:36:53 PM
CHEMIST
PM to prepare AP letter