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APPLICATION NUMBER:

18-086 / S-060

CHEMISTRY REVIEW(S)



Food & Drug Administration

Memorandum

Date : December 10, 2002

From: Linda Ng, Ph.D.,
Chemistry Team Leader, HFD-550

Subject: NDA 18-086 (Timoptic Ophthalmic Solution), Merck & Co

To: The File

Background

NDA 18-086, Timoptic Ophthalmic Solution, was approved in August 1978. During a recent labeling review, the firm was informed to include osmolality in the description of the package insert. Firm submitted a supplement SCS-060 to comply.

Content

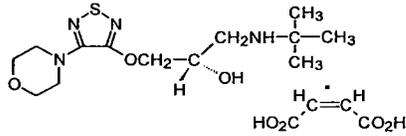
Firm proposed to include osmolality for release testing of the drug product with support data from 177 batches. Reviewer Allan Fenselau recommended approvable because firm disagreed to include testing of osmolality in stability studies. All currently approved products contain osmolality testing during stability because the test is an indicator of water loss from the container.

This memo serves to over-ride the reviewer's recommendation. Input from Medical indicates that Timoptic is safe and effective from 0.25 to 0.5%. The increase in osmolality, if it occurs, will not affect the quality of the product. According to firm, water loss is less than 2% in 24 months. In addition, this is a 24 year old product. All products should be considered on a case-by-case basis.

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/s/

Linda Ng
12/10/02 09:54:32 AM
CHEMIST
PM to prepare AP letter for SCS-060

Chemistry Review Review #1	1. Division HFD-550	2. NDA Number 18-086
3. Name and Address of Applicant Merck & Co., Inc. P.O. 4, BLA-20 West Point, PA 19486 Contact: Virginia G. Snyder, Mgr. Regulatory Affairs		4. Supplement Number Date SCS-060 11-JUN-02
5. Name of Drug TIMOPTIC™ 0.25% & 0.5%	6. Nonproprietary Name	Timolol maleate
7. Supplement Provides for: Addition of a regulatory specification for osmolarity CHANGES BEING EFFECTED-0		8. Amendment(s)
9. Pharmacological Category Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma	10. How Dispensed Rx Topical (eye)	11. Related Documents
12. Dosage Form Ophthalmic Solution (Sterile)	13. Potency(ies)	Timolol maleate, 3.4 & 6.8 mg/mL
14. Chemical Name and Structure see USAN		
 <div style="display: inline-block; vertical-align: top; margin-left: 20px;"> <p>$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ Mol. Wt.: 432.50 2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (S)-, (Z)-2-butenedioate (1:1) salt CAS-26921-17-5</p> </div> <p style="text-align: center;"><u>TIMOLOL MALEATE</u></p>		
<div style="border: 1px solid black; width: 100%; height: 100%;"></div>		
16. Conclusions and Recommendations: Based on consideration of these chemistry, manufacturing and controls issues, the request to can be recommended for APPROVABLE.		
in the USP were forwarded to the sponsor on 29-OCT-02, but as of 18-NOV-02 the sponsor has not produced a response.		
17. Name Allan Fenselau, Review Chemist	Signature	Date
Concurrence Linda Ng, Chemistry Team Leader	Signature	Date

cc: NDA 18-086

HFD-550/Division File

HFD-550/CSO/M.Puglisi

HFD-550/CHEM/A.Fenselau

Doc ID: n18086s.060

HFD-550/CHEM/TeamLdr/L.Ng

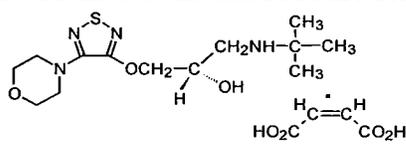
HFD-550/SMO/W.Chambers

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/s/

Allan Fenselau
11/18/02 04:13:45 PM
CHEMIST

Linda Ng
11/20/02 11:47:35 AM
CHEMIST
PM to prepare AE letter if firm did not respond

Chemistry Review Review #2	1. Division HFD-550	2. NDA Number 18-086
3. Name and Address of Applicant Merck & Co., Inc. P.O. 4, BLA-20 West Point, PA 19486 Contact: Virginia G. Snyder, Mgr. Regulatory Affairs		4. Supplement Number Date SCS-060 11-JUN-02
5. Name of Drug TIMOPTIC™ 0.25% & 0.5%	6. Nonproprietary Name	Timolol maleate
7. Supplement Provides for: Addition of a regulatory specification for osmolarity CHANGES BEING EFFECTED-0		8. Amendment(s) BC 22-NOV-02
9. Pharmacological Category Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma	10. How Dispensed Rx Topical (eye)	11. Related Documents
12. Dosage Form Ophthalmic Solution (Sterile)	13. Potency(ies) Timolol maleate, 3.4 & 6.8 mg/mL	
14. Chemical Name and Structure see USAN		
 <p style="text-align: center;">TIMOLOL MALEATE</p>		
<p style="text-align: right;">C₁₃H₂₄N₄O₃S•C₄H₄O₄ Mol. Wt.: 432.50 2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (S)-, (Z)-2-butenedioate (1:1) salt CAS-26921-17-5</p>		
<div style="border: 1px solid black; width: 100%; height: 100%;"></div>		
16. Conclusions and Recommendations: Based on a consideration of chemistry, manufacturing and controls issues, the request to add Osmolarity to the regulatory specification for only product release for TIMOPTIC Ophthalmic Solution (timolol maleate), 0.25% and 0.5% is APPROVABLE.		
17. Name Allan Fenselau, Review Chemist	Signature	Date
Concurrence Linda Ng, Chemistry Team Leader	Signature	Date

cc: NDA 18-086

HFD-550/Division File

HFD-550/CSO/M.Puglisi

HFD-550/CHEM/A.Fenselau

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HFD-550/CHEM/TeamLdr/L.Ng

HFD-550/SMO/W.Chambers

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/s/

Allan Fenselau
12/9/02 05:59:32 PM
CHEMIST

Linda Ng
12/10/02 08:56:23 AM
CHEMIST
See Memo to File for over-ride of reviewer's recommendation.
PM to prepare an AP letter

CHEMIST'S REVIEW # 3	1. ORGANIZATION HFD-550	2. NDA Number(s) 18-086
3. Name and Address of Applicant (City & State): Merck & Co., Inc. P.O. 4 Sumneytown Pike, BLA-20 West Point, PA 19486 (Virginia Snyder at telephone 484-344-7984)		4. AF No.
		5. Supplement(s) Number(s) Date(s) SCS060 11-Jun-2002
6. Drug Name: TIMOPTIC™ Ophthalmic Solution	7. Nonproprietary Name: timolol maleate	8. Amendments & Other (reports, etc.) - Dates SCS060/AF 27-Jun-2003
9. Supplement Provides For: the addition of pH and osmolarity to the label in the DESCRIPTION section and a full description of the product 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): Solution	Potency(ies): 0.25%, 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
17. Comments: In response to a comment in the FDA Approvable Letter dated 11/11/02 and 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™. These changes include the addition of pH and osmolarity in the DESCRIPTION section and descriptive information of the product container and fill size in the HOW SUPPLY section. This is acceptable.		
18. Conclusions and Recommendations: From CMC viewpoint and based on the information submitted this supplement is recommended for an approval action CC: Original NDA# 18-086 HFD-550/Division File HFD-550/Med/Wchambers HFD-550/LNg HFD-550/CSO/MPuglisi HFD-550/YLu R/D initialed by : Linda Ng		
19. REVIEWER		
Name: Yong-de Lu Ph.D.	Signature:	Date Completed: 03-Dec-2003

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/s/

Yong-De Lu
12/3/03 04:08:27 PM
CHEMIST

Linda Ng
12/3/03 05:35:23 PM
CHEMIST
PM to prepare AP letter after labeling review.