

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-963**

MEDICAL REVIEW(S)

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**APPEARS THIS WAY
ON ORIGINAL**

3 Material Reviewed

NDA Volumes 1, 18 through 33

4 Chemistry/Manufacturing Controls

Timolol Ophthalmic
Gel Forming Solution
0.25% 0.5%

Timolol Maleate	Active
Benzododecinium Bromide	Preservative
Gellan Gum	
Xanthan Gum	
Tromethamine	
Boric Acid	
Mannitol	
Polysorbate 80	
Purified Water	Diluent

Reviewer's Comments: *It is not clear why the limits of benzododecinium bromide*

5 Animal Pharmacology/Toxicology*No specific issues noted.*

NDA 20-963 Timolol Maleate Ophthalmic Gel Forming Solution, 0.25% and 0.5%

6 Clinical Background**6.1 Relevant human experience**

Timolol Solution 0.5% and 0.25% have been marketed since 1978.

6.2 Important information from related INDs and NDAs

The following NDAs have been approved:

Timoptic 0.25% and 0.5%	timolol solution	NDA 18-086
Blocadren	timolol tablets	NDA 18-017
Timoptic XE 0.25% and 0.5%	timolol gel forming solution	NDA 20-330

Timoptic 0.5% is indicated for elevated intraocular pressure. The approved dosing regimen for the 0.25% concentration is bid and for 0.5% concentration is qd or bid.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

No clinical pharmacology studies were conducted with Timolol Gel Forming Solution 0.25% and 0.5%. Reference is made to NDA 18-086 and NDA 20-330.

6.5 Other relevant background information

"The majority of the preclinical and clinical information in support of the safety and efficacy of this drug product are based on published literature and studies conducted by Merck in support of Timoptic-XE Ophthalmic Gel Forming Solution (NDA 20-330), Timoptic Ophthalmic Solution (NDA 18-086) and Blocadren tablets (NDA 18-017). This application is submitted under Section 505(b)(2) since the studies relied upon by the applicant were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the persons who conducted the investigations.

6.6 Proposed Directions for Use

The dose is one drop of timolol maleate ophthalmic gel forming solution (either 0.25% or 0.5%) in the affected eye(s) once daily.

**APPEARS THIS WAY
ON ORIGINAL**

7 Description of Clinical Data Sources

Principal Studies

Review Number	Protocol Number	Design	Doses	Enrolled	Completed (Drop out)	Age Range [years]
1	C-97-03	Multiple dose Double masked Parallel Multicenter 3 months	Timolol GFS 0.25% qd Timoptic 0.25% bid The Timolol GFS group also received placebo qd	65♂ 89♀ 69♂ 87♀	154 (10) 156 (10)	31-86 27-88
2	C-97-04	Multiple dose Double masked Parallel Multicenter 3 months	Timolol GFS 0.5% qd Timolol Sol 0.5% bid The timolol GFS group also received placebo qd	70♂ 88♀ 74♂ 84♀	158 (27) 158 (22)	29-93 35-95
3	C-97-05	Multiple dose Double masked Parallel Multicenter 12 months	Timolol GFS 0.5% qd Timolol Sol 0.5% bid The timolol GS group also received placebo qd	241	Ongoing	

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8 Clinical Studies**8.1 Indication**

Reduction of Intraocular Pressure

8.1.1 Reviewer's Trial # 1

Sponsor's protocol # C-97-03

A Three-Month, Multicenter, Triple-Masked, Parallel Study of the Safety and Efficacy of Timolol Gel Forming Solution 0.25%, Dosed Once-Daily, Compared to Timoptic 0.25% Ophthalmic Solution, Dosed Twice-Daily, in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension

8.1.1.1 Objective/Rationale

To evaluate the safety and IOP-lowering efficacy of Timolol GFS 0.25%, dosed once-daily, compared to Timoptic 0.25% Ophthalmic Solution, dosed twice-daily, in patients with primary open-angle glaucoma or ocular hypertension

8.1.1.2**Design**

Parallel, double-masked, active-controlled, randomized study

8.1.1.3 Protocol

	Screen	Eligibility 1		Eligibility 2		Day 1	Week 1	Week 2		Month 1		Month 2		Month 3	
		8am	10am	8am	10am	8am	8am	8am	10am	8am	10am	8am	10am	8am	10am
Medical History	X														
Pupil Diameter				X											X
Best corrected visual acuity	X	X		X		X	X	X		X		X			X
Biomicroscopy	X	X		X		X	X	X		X		X			X
Dilated Fundus Exam	X														X
Gonioscopy	X														
Automated Perimetry			X												X
Pregnancy Test	X														X
IOP		X	X	X	X			X	X	X	X	X	X	X	X
Resting pulse	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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8.1.1.3.1 Population

Men or women with intraocular pressure after washout of 24-36 mmHg in one or both eyes. The Baseline IOP was measured at each of two eligibility visits at least one week apart..

8.1.1.3.2 Endpoints

Efficacy - IOP
Safety - Cup to disc ratio, visual acuity, visual field, blood pressure, heart rate, ocular signs and symptoms, and incidence of adverse experiences.

8.1.1.3.3 Statistical considerations

Randomization was equal between groups. There were no formal interim analyses. There were no covariate adjustments.

**APPEARS THIS WAY
ON ORIGINAL**

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

	Investigator	Location	Intent-to-Treat/Per-Protocol	
			Timolol-GFS 0.25%	Timolol-.25%
271	Robert Stewart, MD	Houston, TX	12/12	12/12
470	Donald Brotheman, MD	Dallas, TX	11/11	11/11
479	Robert Allen, MD	Richmond, VA	0/0	1/1
697	George Tate, MD	Charlotte, NC	2/2	1/1
943	Robert Laibovitz, MD	Austin, TX	27/27	28/28
1007	Thomas Walters, MD	Austin, TX	15/14	15/15
1008	Barry Horwitz, MD	Houston, TX	0/0	0/0
1037	Michael Lamensdorf, MD	Sarasota, FL	0/0	1/1
1208	Robert Caine, MD	Fredericksburg, VA	10/10	9/9
1229	James Crabb, MD	Memphis, TN	8/8	8/8
1240	Robert Whitaker, MD	Irving, TX	2/2	3/2
1473	Thomas Mundorf, MD	Charlotte, NC	10/10	10/9
1552	Carl Camras, MD	Omaha, NE	9/9	8/8
1611	Mark Sherwood, MD	Gainesville, FL	9/9	8/8
1733	Donald McCurdy, MD	Birmingham, AL	8/8	9/9
1913	Jeffrey Wasserstrom, MD	La Mesa, CA	13/13	12/10
1930	Robert Friedman, MD	Sunrise, FL	6/6	6/6
1952	Kevin Greenidge, MD	New York, NY	2/2	2/2
1964	Ramesh Tripathi, MD	Columbia, SC	1/1	2/2
1992	Talya Kupin, MD	Detroit, MI	7/6	6/6
2163	Daniel Messner, MD	Southern Pines, NC	1/1	2/2
2176	Brock Bakewell, MD	Tucson, AZ	1/0	2/2
	Total		154/151	156/152

Reviewer's Comments: *Thomas Mundorf's address should be corrected (Zip Code incorrect).*

Intent to Treat

		Timolol GFS Number (%)	Timolol Solution Number (%)
Gender	Female	89 (58)	87 (56)
	Male	65 (42)	69 (44)
Race	White	104 (67)	106 (68)
	Black	38 (24)	30 (19)
	Other	12 (8)	20 (13)
Iris Color	Brown	86 (55)	93 (60)
	Hazel	20 (13)	18 (10)
	Green	5 (3)	7 (5)
	Blue	41 (27)	36 (24)
	Grey	2 (1)	2 (1)
Age	Mean	62.7	63.2
	Range	31-86	27-88

Reviewer's Comments: *There were no significant differences between groups.*

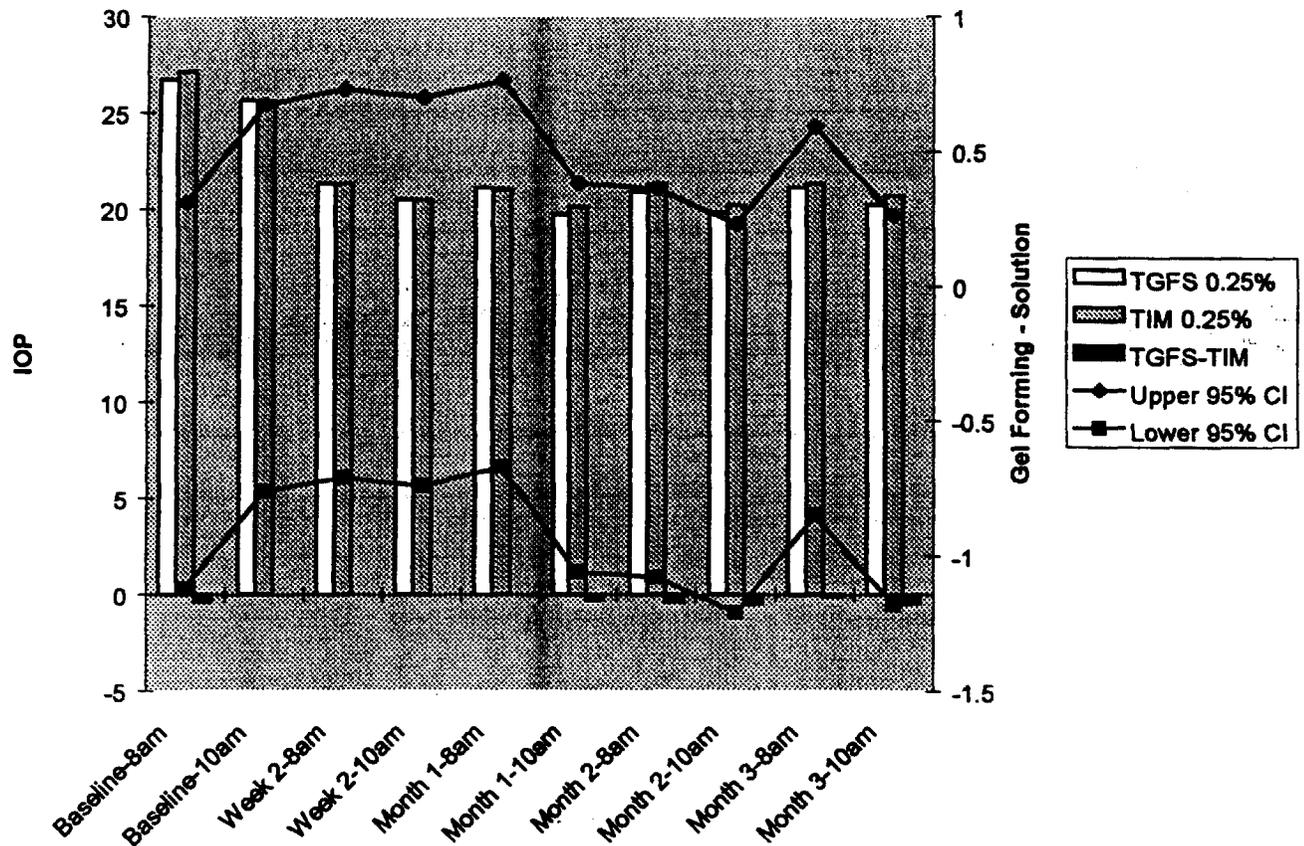
Discontinued for Adverse Experiences

<u>Invest</u>	<u>Patient</u>	<u>Treatment</u>	<u>Day of Day</u>		<u>Reason</u>
			<u>Onset</u>	<u>Discontinued</u>	
1992	1912	Timolol GFS	1	2	Blurred vision, tearing
1611	2405	Timolol GFS	41	48	Keratitis
0271	2502	Timolol GFS	4	4	Back pain
1240	3001	Timolol 0.25%	30	58	Blurred vision, itching, headache
1473	2306	Timolol 0.25%	7	7	Lung Disorder
1229	1501	Timolol 0.25%	28	30	Retinal Hemorrhage
1913	2909	Timolol 0.25%	29	36	Macular edema

Reviewer's Comments: *No significant new events.*

8.1.1.4.2 Efficacy endpoint outcomes

C-97-03 IOP Per Protocol Analysis

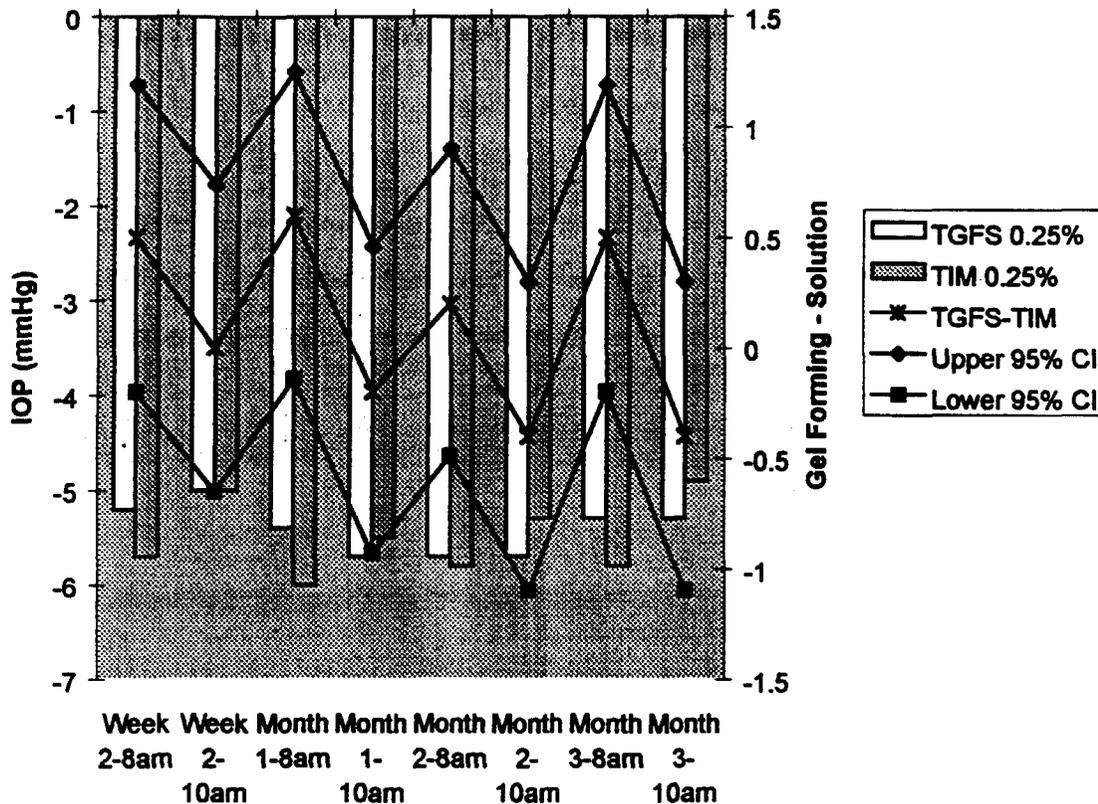


n=144 for TGFS (timolol gel forming solution) at Month 3

n=146 for Timolol Solution at Month 3

Reviewer's Comments: *The IOP reductions are considered equivalent. The intent to treat analysis was essentially the same.*

C-97-03 Change from Baseline - Intent to Treat



Reviewer's Comments:

The definition used for equivalence in this review is:

- Confidence interval includes 0; and*
- Confidence interval is no greater than ± 1 for most intervals; and*
- Confidence interval is no greater than ± 1.5 .*

Equivalence of timolol gel forming solution with timolol solution has been established.

Additional Analyses:

Sex: At several timepoints, men showed a larger decrease in mean IOP than women, regardless of treatment.

Race: There were no significant differences between races.

Iris color: At several timepoints, light colored irides showed a larger decrease in mean IOP than dark colored irides, regardless of treatment.

Reviewer's Comments: *The differences in response with respect to iris color have been observed before.*

8.1.1.4.3 Safety outcomes**Lines of Visual Acuity Change - Baseline to Final Visit**

	≥+2 Lines	+1 Line	No Change	-1 Line	≥-2 Lines
GFS	1	9	104	31	9
Timolol solution	2	3	112	31	8

Reviewer's Comments: *There are no clinically significant differences with respect to visual acuity.*

Cup to Disk Ratio

	Baseline	Change at Exit
GFS	0.446	-.002
Timolol Solution	0.437	.004

Reviewer's Comments: *There are no clinically significant differences with respect to cup to disc ratios.*

Visual field (Humphrey) dB

	Baseline Mean Deviation	Change at Exit
Timolol GFS	-1.95	-.03
Timolol Solution	-2.64	.60

Reviewer's Comments: *There are no clinically significant differences with respect to visual field.*

Vital Signs

Reviewer's Comments: *There were the typical reductions in heart rate and blood pressure in each group.*

Patients reporting Adverse Experiences (>1%)

	<u>GFS</u>	<u>Solution</u>
Blurred vision	9 (6%)	3 (2%)
Headache	8 (5%)	3 (2%)
Hyperemia	5 (3%)	1 (1%)
Discomfort	3 (2%)	2 (1%)
Pruritis	3 (2%)	2 (1%)
Blepharitis	3 (2%)	1 (1%)
Rhinitis	3 (2%)	2 (1%)

Reviewer's Comments: *The differences in blurred vision should be considered significant.*

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8.1.2 Reviewer's Trial # 2**Sponsor's protocol #**

8.1.2.1	Objective/Rationale	Same as Study #1 except using 0.5%
8.1.2.2	Design	Same as Study #1 except using 0.5%
8.1.2.3	Protocol	Same as Study #1
8.1.2.3.1	Population	Same as Study #1
8.1.2.3.2	Endpoints	Same as Study #1
8.1.2.3.3	Statistical considerations	Same as Study #1

**APPEARS THIS WAY
ON ORIGINAL**

8.1.2.4.1 Populations enrolled/analyzed

	Investigator	Location	Intent-to-Treat/ Per-Protocol	
			Timolol- GFS .5%	Timolol- .5%
331	Alan Mandell, MD	Memphis, TN	11/5	11/11
355	Michael Kottler, MD	Salt Lake City, UT	7/6	6/5
432	Norman Levy, MD	Gainesville, FL	2/2	2/2
750	Kenneth Olander, MD	Milwaukee, WI	6/4	7/6
884	Don Minckler, MD	Los Angeles, CA	1/1	0/0
1064	Steven Simmons, MD	Albany, NY	6/6	5/5
1212	Michael Stiles, MD	Kansas City, MO	9/7	8/6
1237	Lawrence M. Hurvitz, MD	Sarasota, FL	4/3	3/2
1300	Kerry Assil, MD	Santa Monica, CA	1/1	0/0
1403	Jeffrey Morris, MD	Oceanside, CA	12/12	12/12
1409	Dong Shin, MD	Detroit, MI	9/9	9/8
1598	George A. Cioffi, MD	Portland, OR	1/1	1/0
1782	Miles Galin, MD	New York, NY	11/11	11/11
1806	Kenneth Sall, MD	Bellflower, CA	29/29	28/27
1948	Beth Friedland, MD	Research Triangle Park, NC	3/3	4/4
1971	G. Richard Cohen, MD	Boca Raton, FL	7/7	7/7
1972	Onex Stevenson, MD	New Orleans, LA	11/11	11/9
1973	Cecil C. Beehler, MD	Fort Meyers, FL	3/2	4/2
1975	Carl B. Tubbs, MD	Stillwater, MN	6/5	7/7
1985	Margaret DiGaetano, MD	Daytona Beach, FL	1/1	1/1
1999	Marta Lopatynsky, MD	Bayonne, NJ	3/2	4/4
2132	Joseph Armstrong, MD	Bristol, TN	1/1	2/2
2135	Ernest Howerton, MD	Austin, TX	0/0	0/0
2136	Marvin Greenberg, MD	Tamarac, FL	5/4	5/5
2137	Ronald Frenkel, MD	Stuart, FL	1/1	2/2
2150	Allan Greenberg, MD	Miami Shores, FL	5/5	5/5
2158	Martin B. Wax, MD	St. Louis, MO	2/2	2/2
2174	Karanjit Kooner, MD	Dallas, TX	1	1
	Total		158/140	158/145

Reviewer's Comments: *Information on the number of patients in the Per-protocol analysis for investigator 2174 should be included.*

Intent to Treat

		Timolol GFS Number (%)	Timolol Solution Number (%)
Gender	Female	88 (56)	84 (53)
	Male	70 (44)	74 (47)
Race	White	131 (83)	121 (77)
	Black	19 (12)	29 (18)
	Other	8 (5)	8 (5)
Iris Color	Brown	72 (46)	84 (53)
	Hazel	27 (17)	21 (13)
	Green	9 (6)	4 (2)
	Blue	50 (32)	47 (30)
	Grey	0 (0)	2 (1)
Age	Mean	67.7	65.2
	Range	29-93	35-95

Reviewer's Comments: *There were no significant differences between groups.*

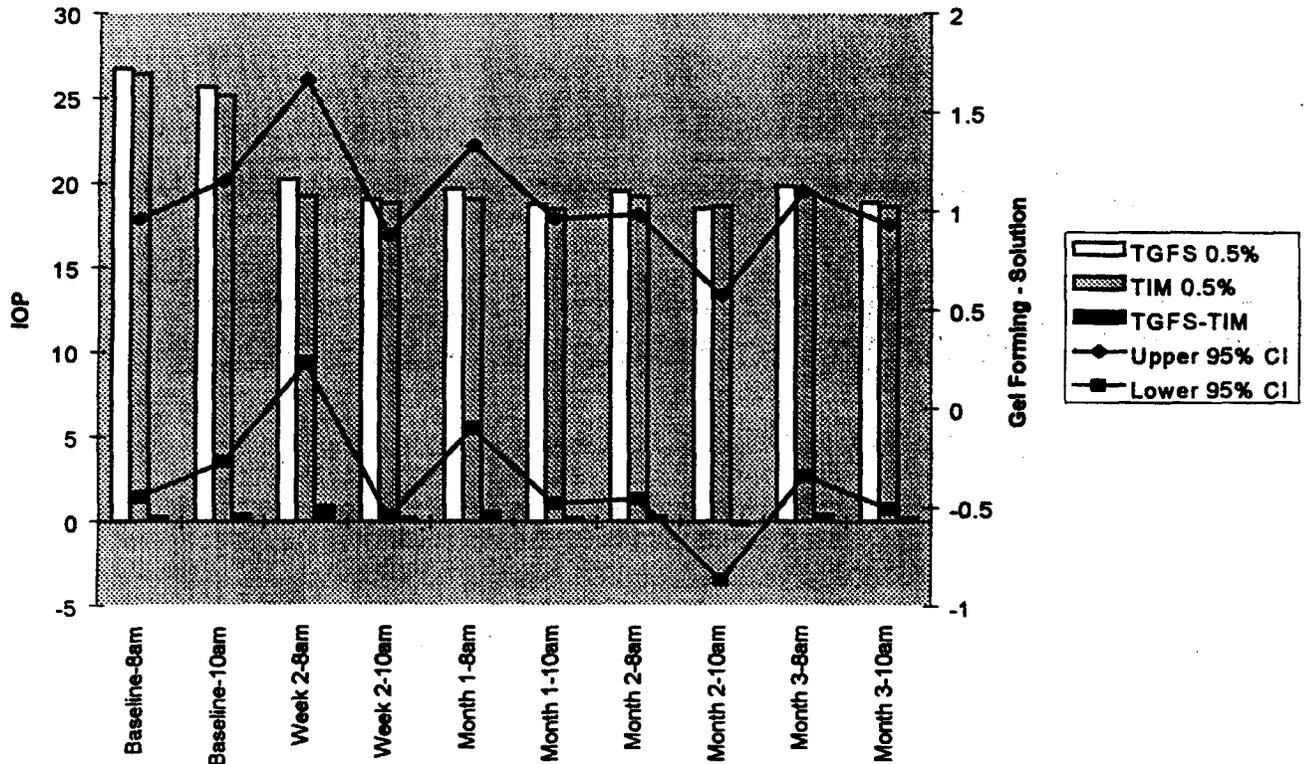
Discontinued for Adverse Experiences

<u>Invest</u>	<u>Patient</u>	<u>Treatment</u>	<u>Day of Day</u>		<u>Reason</u>
			<u>Onset</u>	<u>Discontinued</u>	
355	6208	Timolol GFS	53	53	Retinal hemorrhage
1403	6524	Timolol GFS	9	9	Hypesthesia and Tinnitus
1782	5608	Timolol GFS	17	19	Pruritis and facial edema
1806	6937	Timolol GFS	2	2	Atrial fibrillation
1806	6957	Timolol GFS	10	10	Cellulitis
2158	7404	Timolol GFS	45	45	Contact dermatitis
1403	6502	Timolol Solution	40	43	Hypotension
1403	6514	Timolol Solution	19	28	Headaches and sweating
1598	5402	Timolol Solution	57	60	Asthma and bronchitis
2150	5709	Timolol Solution	3	3	Myocardial infarction

Reviewer's Comments: *No significant new events.*

8.1.2.4.2 Efficacy endpoint outcomes

C-97-04 IOP Per Protocol Analysis

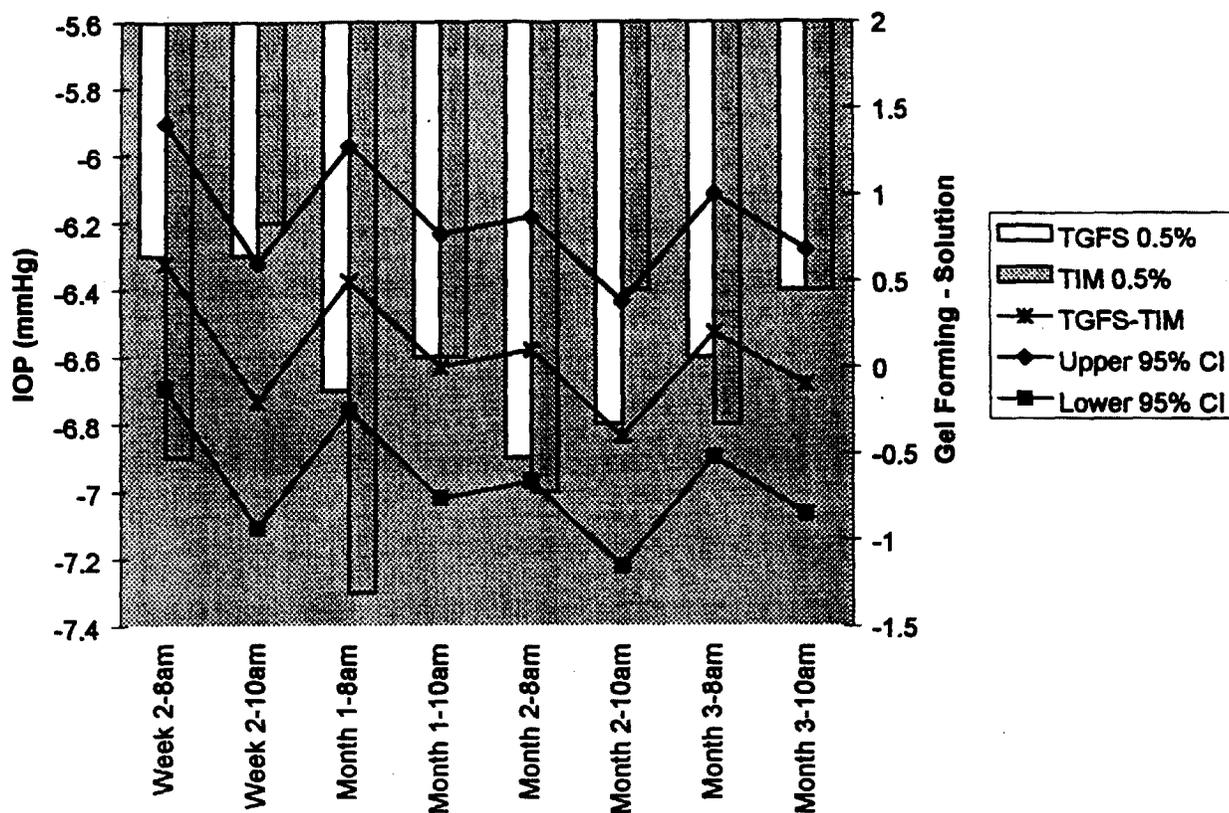


n=131 for TGFSF (timolol gel forming solution) at Month 3
n=136 for Timolol Solution at Month 3

Reviewer's Comments:

The IOP reductions are almost considered equivalent. The majority of the 95% confidence interval values are less than 1, but one of the confidence intervals exceeds 1.5. The intent to treat analysis was essentially the same.

C-97-04 Change from Baseline - Intent to Treat



Reviewer's Comments:

The definition used for equivalence in this review is:

- Confidence interval includes 0; and*
- Confidence interval is no greater than ± 1 for most intervals; and*
- Confidence interval is no greater than ± 1.5 .*

Equivalence of timolol gel forming solution with timolol solution has been established.

Additional Analyses:

- Sex:** At several timepoints, men showed a larger decrease in mean IOP than women, regardless of treatment.
- Age:** There were no significant differences in different age groups.
- Race:** There were no significant differences between races.
- Iris color:** At a few timepoints, light colored irides showed a larger decrease in mean IOP than dark colored irides, regardless of treatment.

Reviewer's Comments: *The differences in response with respect to iris color have been observed before.*

8.1.2.4.3 Safety outcomes**Lines of Visual Acuity Change - Baseline to Final Visit**

	≥+2 Lines	+1 Line	No Change	-1 Line	≥-2 Lines
GFS	4	15	99	34	6
Timolol solution	0	6	118	27	7

Reviewer's Comments: *There are no clinically significant differences with respect to visual acuity.*

Cup to Disk Ratio

	Baseline	Change at Exit
GFS	0.406	-.001
Timolol Solution	0.398	.004

Reviewer's Comments: *There are no clinically significant differences with respect to cup to disc ratios.*

Visual field (Humphrey) dB

	Baseline Mean Deviation	Change at Exit
Timolol GFS	-2.97	-.08
Timolol Solution	-2.07	-.10

Reviewer's Comments: *There are no clinically significant differences with respect to visual field.*

Vital Signs

Reviewer's Comments: *There were the typical reductions in heart rate and blood pressure in each group.*

Patients reporting Adverse Experiences (>1%)

	<u>GFS</u>	<u>Solution</u>
Infection	8 (5%)	2 (1%)
Discomfort	6 (4%)	4 (3%)
Blurred vision	4 (3%)	2 (1%)
Hypertension	4 (3%)	5 (3%)
Pruritis	3 (2%)	2 (1%)
Edema	3 (2%)	0
Blepharitis	3 (2%)	0
Headache	2 (1%)	3 (2%)
Foreign body sensation	2 (1%)	0
Conjunctival cyst	2 (1%)	0
Retinal hemorrhage	2 (1%)	0
Pain	2 (1%)	4 (3%)
Dyspepsia	2 (1%)	1 (1%)
Arthritis	2 (1%)	1 (1%)
Rhinitis	2 (1%)	1 (1%)
Pharyngitis	2 (1%)	0
Hyperemia	1 (1%)	5 (3%)

Reviewer's Comments: *The differences in blurred vision should be considered significant.*

**8.1.3 Reviewer's Trial # 3
Sponsor's protocol # C-97-05**

8.1.3.1 Objective/Rationale

8.1.3.2 Design Same as Study #1 except for duration (12 weeks for this trial)

8.1.3.3 Protocol Same as Study #1 except for duration

8.1.3.3.1 Population Same as Study #1

8.1.3.3.2 Endpoints Same as Study #1

8.1.3.3.3 Statistical considerations Same as Study #1 except that there are an equal number of subjects per group.

8.1.3.4 Results

Summary of Ongoing Timolol Gel Forming Solution Clinical Studies

Protocol Number	Study Description	Treatment Groups	Number of Patients Randomized/Planned to Complete	Study Status
C-97-05	12-month safety/efficacy trial for Timolol Gel Forming Solution 0.5% Triple-Masked, Randomized	-Timolol Gel Forming Solution 0.5%, QD -Timoptic XE 0.5%, QD	241/150	In Progress

Summary of Results of Ongoing Clinical Trial (C97-05)

The masked safety data generated from C-97-05 through May 29, 1998 are summarized as follows.

Adverse Events Occurring in C-97-05

Timolol Gel Forming Solution 0.5% or Timoptic XE 0.5%	
N=241	
Adverse Events	Frequency
Ocular	
Hyperemia Eye	11
Discomfort Eye	9
Vision Blurred	8
Blepharitis	6
Tearing	6
Conjunctivitis	5
Dry Eye	5
Keratitis	5
Lid Margin Crusting	5
Pain Eye	5
Pruritus Eye	4
Vision Abnormal	4
Cataract	3
Pingueculum	3
Brow ache	2
Edema Conjunctival	2
Edema Lid	2
Foreign Body Sensation	2
Keratopathy	2
Staining Corneal	2
Surgical/Medical Procedure	2
Vision Decrease	2
Visual Acuity Decrease	2
Vitreous Disorder	2
Capsular Opacity	1
Cataract NOS	1
Corneal Erosion	1
Corneal Lesion	1
Diplopia	1
Discharge Eye NOS	1
Eye Disorder	1
Follicles Conjunctival	1
Glare	1
Hemorrhage Retinal	1
Hemorrhage Subconjunctival	1
Iritis	1
Meibomitis	1
Optic Nerve Disorder	1
Ptosis	1

Timolol Gel Forming Solution 0.5% or Timoptic XE 0.5%	
N=241	
Adverse Events	Frequency
Spasm Lid	1
Thrombosis Retinal Vein	1
Vitreous Detachment	1
Nonocular	
Body As A Whole	
Cold Syndrome	10
Headache	9
Infection	8
Surgical/Medical Procedure	7
Allergy	4
Flu Syndrome	4
Pain	4
Pain Back	2
Hernia	1
Injury Accidental	1
Pain Abdomen	1
Pain Chest	1
Cardiovascular System	
Hypertension	15
Bradycardia	1
Cardiovascular Disorder	1
Coronary Artery Disease	1
Digestive System	
GI Disorder	2
Diarhea	1
Dyspepsia	1
Nausea	1
Rectal Disorder	1
Stomatitis	1
Vomit	1
Endocrine System	
Diabetes Mellitus	1
Hemic and Lymphatic System	
Anemia	1
Metabolic and Nutritional Disorders	
Hypercholesteremia	4
Edema Peripheral	3
Hypokalemia	2
Dehydration	1
Obesity	1

Timolol Gel Forming Solution 0.5% or Timoptic XE 0.5%	
N=241	
Adverse Events	Frequency
Musculo-Skeletal System	
Arthritis	2
Bone Fracture Spontaneous	1
Myalgia	1
Myopathy	1
Osteoporosis	1
Tendon Disorder	1
Nervous System	
Depression	4
Anxiety	3
Dizziness	1
Neuralgia	1
Paralysis Facial	1
Somnolence	1
Respiratory System	
Sinusitis	7
Rhinitis	5
Pharyngitis	4
Bronchitis	2
Lung Disorder	2
Dyspnea	1
Emphysema	1
Epistaxis	1
Pneumonia	1
Skin and Appendages	
Dermatitis	2
Herpes Zoster	2
Acne	1
Angioedema	1
Carcinoma Skin	1
Dermatitis Contact	1
Erythema	1
Hypertrophy Skin	1
Pruritus	1
Psoriasis	1
Skin Disorder	1
Skin Dry	1
Special Senses	
Otitis Externa	1
Otitis Media	1
Urogenital System	
Carcinoma Prostate	2

Timolol Gel Forming Solution 0.5% or Timoptic XE 0.5%	
N=241	
Adverse Events	Frequency
Cystitis	1
Infection Urinary Tract	1
Kidney Calculus	1
Prostate Disorder	1

Deaths

No death reports have been received.

Patients Discontinued Due To Adverse Events in C-97-05

Inv.	Pt	Age	Sex	Event	Onset Day	Intensity	Duration	Outcome
1903	104	47	F	Follicles Conjunctival, Dermatitis Contact	2	Mild	13 Days	Resolved
2182	1923	73	M	Blepharitis	1	Moderate	11 Days	Resolved
1011	804	78	F	Emphysema	203	Moderate	NA	Continuing
1011	809	71	F	Vitreous Disorder ^a	36	Mild	NA	Continuing
2182	1921	71	F	Vision Blurred, Iritis	128	Moderate	NA	Resolved
1011	810	64	M	Arthritis	73	Mild	NA	Continuing
1011	811	80	F	Surgical/Medical Procedure ^b	260	Moderate	1 Hour	Resolved
2128	1522	70	F	Hypertension	71	Moderate	11 Days	Continuing

^aEvent Occurred Intermittently

NA = Not Available

^a floaters with no retinal hole

^b tooth extraction

APPEARS THIS WAY
ON ORIGINAL

9. Summary of Efficacy

Equivalence in IOP reduction has been demonstrated between timolol maleate ophthalmic solution 0.25% and timolol maleate ophthalmic gel forming solution 0.25% in Study #1.

Equivalence in IOP reduction has been demonstrated between timolol maleate ophthalmic solution 0.5% and timolol maleate ophthalmic gel forming solution 0.5% in Study #2.

10. Summary of Safety

The safety profile of this product is generally equivalent to other timolol maleate ophthalmic gel forming solutions.

**APPEARS THIS WAY
ON ORIGINAL**

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

13 pages
Drott Labeling

12 Conclusions

1. The submitted studies support the bioequivalence of Timoptic gel forming solution (0.5%) administered once a day and timolol solution (0.5%) administered twice a day.
2. The submitted studies support the bioequivalence of Timoptic gel forming solution formulation (0.25%) administered once a day and timolol solution formulation (0.25%) administered twice a day.
3. Labeling revisions are recommended.

The following issues should be clarified or revised:

1. *It is not clear why the limits of benzododecinium bromide are 80-120 when they probably should be 90-110%.*
2. *Thomas Mundorf's address should be corrected (Zip Code incorrect).*
3. *Information on the number of patients in the Per-protocol analysis for investigator 2174 in Study C-97-04 should be included.*
4. *An explanation for the column titled "Days" in section 16.2.1 of Study Report C-97-04 should be provided.*
5. *Labeling as described in this review.*

**APPEARS THIS WAY
ON ORIGINAL**

13 Recommendations

Timolol Maleate Gel Forming Solution, 0.25% and 0.5% (NDA 20-963) is recommended for approval when indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension and open-angle glaucoma on the condition that the labeling is modified as outlined in this review.

WAC 8/13/98

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-963
HFD-550
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-830/CHEM/Uppoor
HFD-805/MICRO/Stinavage
HFD-550/PHARM/Coulter
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL

**Medical Officer's Review of NDA 20-963
Amendment**

NDA 20-963
M.O. Review #2

Submission dates: 8/18/98 & 8/25/98
Review completed: 9/4/98

Name: Timolol Maleate Ophthalmic Gel Forming Solution, 0.25% and 0.5%

Chemical name: (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol,(Z)-2-butenedioate (1:1) salt.

Sponsor: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099
(817) 551-8512

Pharmacologic Category: Non-selective β -adrenergic receptor blocking agent

Proposed Indication(s): Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma

Dosage Form: Gel-forming solution

Submitted: Responses to the additional clinical issues and the request for revised labeling presented in telephone call of August 10, 1998.

1. Alcon agrees to utilize the "yellow" cap color for both the 0.5% and 0.25% concentrations in domestically marketed product.

Reviewer's Comments: *Acceptable.*

2. **Issue:** It is not clear why the limits of benzododecinium bromide are

Response: The specification range of _____ has been historically established based upon recognized losses of _____ when _____ are _____ In addition, the assays historically have had a relative higher assay variability due to the assay methodology as well as the low concentration of preservative in the formulation. The safety of the upper range of the specification range has been biologically qualified through a QID dosed six month rabbit study where BDB was present at 0.016% in a formulation of diclofenac sodium ophthalmic solution (NDA 20809 page 5-002

SN:003 page 8-0022 of February 29,1996). The lower limit of has also been tested and passes preservative effectiveness meeting both USP and Ph. Eur. Nevertheless, since Alcon is not utilizing an overage for the preservative in this formulation, we would be willing to reduce the upper limit to of label.

Reviewer's Comments: *Data based on a formulation of diclofenac in rabbits is not relevant to the timolol maleate gel forming solution. The applicant should commit to a revised specification range.*

3. **Issue:** Thomas Mundorf's address should be corrected (Zip Code incorrect).
Response: The correct address for Investigator # 1473, Thomas Mundorf is:

Thomas Mundorf, M.D.
Presbyterian Medical Center
1718 East 4th Street, Suite 902
Charlotte, NC 28204

Reviewer's Comments: *Acceptable.*

4. **Issue:** Information on the number of patients in the Per-Protocol analysis for investigator 2174 in study C-97-04 should be provided.

Response: Information on the number of patients in the per-protocol analysis for investigator # 2174, Dr. Karanjit Kooner, was omitted from the table since there were no efficacy evaluable patients. Table 1 showing the number of per-protocol patients per investigator, including the patients for this investigator (# 2174), is provided.

Reviewer's Comments: *Acceptable.*

5. **Issue:** An explanation for the column titled 'Days' in section 16.2.1 of Study Report C-97-04 should be provided.

Response: The column titled 'days' indicates the number of study days that the patient did not complete in the 90 day study. The number of days that the patient was on study drug can be calculated by subtracting this number from 90.

Reviewer's Comments: *Acceptable.*

6. **Issue:** Revised labeling – See next page

Reviewer's Comments: *Recommended additions and deletions are shown.*

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RELEASABLE

13 pages
Draft Labeling

Deficiencies identified in the Chemistry Review dated 9/2/98:

1. In the regulatory specifications for the drug product, the lower limit of gel strength specification for both strengths of 0.25% and 0.5% Timolol Maleate Ophthalmic Gel Forming Solution should be raised to a number greater than 30 Pascals, which is supported by the content of unhydrolyzed acetate required in xanthan gum for gel formation.

Reviewer's Comments: *Concur with deficiency.*

2. Specification limits of benzododecinium bromide in the drug product should be revised from the proposed of label to of label.

Reviewer's Comments: *The applicant has stated that they are willing to revise the specification but will need to commit to the revision.*

3. Yellow color caps should be used for both strengths of drug product.

Reviewer's Comments: *Addressed in the submission dated August 18, 1998.*

4. The following conditions should be added to the stability protocols:
 - a. The product should be stored in both upright and inverted positions, or, upright and horizontal positions for the first three production lots.
 - b. Three, nine and eighteen months test time points should be included in the ongoing stability program beyond the first three commercial batches.

Reviewer's Comments: *Concur with deficiency.*

5. The proposed proprietary name (trade name) "Timolol Maleate Ophthalmic Gel Forming Solution" stated on Form FDA 356h can not be used as a proprietary name. The CDER Labeling and Nomenclature Committee has recommended "timolol maleate ophthalmic solution, gel forming drops" as the established name for this product.

Reviewer's Comments: *Later submissions of the 356h form including this latest submission, identify Timolol Gel Forming Solution as the established name and do not list a proprietary name. At present, the name should be consistent with the proposed package insert.*

5. An editorial correction from "affect eye(s)" to "affected eye(s)" is required in the USUAL DOSAGE section of carton labels and primary container labels of both 0.25% and 0.5% drug products.

Reviewer's Comments: *This change has already been made.*

7. Storage condition mentioned in the "Proposed Package Insert" and the "Annotated Proposed Package Insert" is "Store between 4° and 25°C (36° and 77°F)". On the immediate container labels and carton labels, it is mentioned as "Store at 39°F to 77°F (4°C and 25°C)". The storage condition mentioned in the package insert, annotated package insert, on immediate container labels and the carton labels should be identical, as "Store between 39°F and 77°F (4°C and 25°C)".

Reviewer's Comments: *The storage conditions will need to match with respect to centigrade and Fahrenheit, i.e., either 2-25°C and 36-77°F, or 4-25°C and 39-77°F.*

8. Information about the distributor or manufacturer of the products, currently mentioned in the primary container labels and the carton labels should also be included in both the proposed package insert and the annotated proposed package insert.

Reviewer's Comments: *The name of the distributor or manufacturer of the product is not required to be in the package insert (21CFR 201.1 and 201.57)*

The following requests for information have been made in the Chemistry Review:

1. According to Timolol Maleate Analytical Reference Standard Summary on page 4-00326 of NDA, the Assay of timolol maleate by
However, according to page 4-00313, Certificate of Analysis for the same material,
Similarly, the loss on drying results stated on page 4-00318 and page 4-00313 do not match. The inconsistency of these results should be explained.

Reviewer's Comments: *Concur.*

2. Data of each replicate measurement (eight individual numbers) should be provided for gel strength testing for stability lot # 5829-05, 5 mL fill in 5 mL containers, after storage at 25°C for 52 weeks, as a representative example of a gel strength test result with a RSD of less than 6% for the individual test results.

Reviewer's Comments: *Concur.*

Additional Manufacturing Comments:

1. Submission of a prior approval supplement will be needed for the extension of expiration date, if the desired extension of expiration date is based upon the stability data of primary stability batches.

Reviewer's Comments: *Concur.*

2. The following two items should be included in the manufacturing batch records:
 - a. Supplemental Formulation Page should be included in the Bulk Product Order Form for the preparation of mannitol/xanthan stock solution.
 - b. Inclusion of a data entry space for noting the F_0 , delivered to the mannitol/xanthan stock solution during compounding.

Reviewer's Comments: *Concur.*

12 Conclusions

1. The submitted studies support the bioequivalence of Timoptic gel forming solution (0.5%) administered once a day and timolol solution (0.5%) administered twice a day.
2. The submitted studies support the bioequivalence of Timoptic gel forming solution formulation (0.25%) administered once a day and timolol solution formulation (0.25%) administered twice a day.
3. Labeling revisions are recommended.
4. The deficiencies and requests for additional information should be forwarded to the applicant.

**APPEARS THIS WAY
ON ORIGINAL**

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13 Recommendations

Timolol Maleate Gel Forming Solution, 0.25% and 0.5% (NDA 20-963) is recommended for approval when indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension and open-angle glaucoma on the condition that the deficiencies listed in this review are satisfactorily addressed.



Wiley A. Chambers, M.D.

Medical Officer, Ophthalmology

cc: NDA 20-963
HFD-550
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-830/CHEM/Uppoor
HFD-805/MICRO/Stinavage
HFD-880/BIOPHARM/Tandon
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

**APPEARS THIS WAY
ON ORIGINAL**

**Medical Officer's Review of NDA 20-963
Amendment**

NDA 20-963
M.O. Review #3

Submission dates: 9/29/98 & 10/13/98
Review completed: 10/20/98

Name: Timolol Maleate Ophthalmic Gel Forming Solution, 0.25% and 0.5%

Chemical name: (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol,(Z)-2-butenedioate (1:1) salt.

Sponsor: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099
(817) 551-8512

Pharmacologic Category: Non-selective β -adrenergic receptor blocking agent

Proposed Indication(s): Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma

Dosage Form: Gel-forming solution

Submitted: Responses to request for revised labeling and additional information presented in telephone calls of September 4, and October 9, 1998.

Revised labeling which makes the following requested editorial corrections.

1. In the first sentence of paragraph 2 on Page 2 of the insert, a comma has been inserted following the word "normal". The sentence now reads "... of reducing elevated, as well as normal, intraocular pressure, .".
2. The legend to the figures presenting the Mean IOP data for the 0.25% study have been revised to correctly identify the study drugs as being the 0.25% concentration.
3. In the last paragraph of the Adverse Reactions section discussing clinical experience with oral timolol maleate, "neuropsychometrics tests" was revised to read "neuropsychometric tests."

Furthermore, in reviewing the draft labeling for the carton and container, it was discovered that the product name was presented incorrectly as "Timolol Maleate Gel Forming Ophthalmic Solution." The name has been corrected to "Timolol Maleate Ophthalmic Gel Forming Solution." Revised draft labeling making this correction is also provided.

Reviewer's Comments: *Acceptable.*

NDA 20-963 Timolol Maleate Ophthalmic Gel Forming Solution, 0.25% and 0.5%

In addition, Alcon Laboratories Inc., agrees to accept the following modifications of the CMC submission:

1. Alcon agrees to revise the specification limits for benzododecinium bromide in the drug product to be 85% to 110% of label. Additionally, Alcon commits to evaluate, over the next 3 years, the appropriateness of the limits for this test based upon additional manufacturing experience at the commercial scale.
2. Alcon agrees to modify our stability protocol commitment of September 29, 1998. Alcon has revised the testing performed on inverted stability samples to be consistent with the tests for upright storage. The revised stability protocol commitment (Part 4.13.10) is provided. Sub-part of this reflects the basis for extending the expiry period based upon full shelf life data generated per this protocol.

Reviewer's Comments: *Acceptable.*

The following issues were identified in the Chemistry Review:

1. As stated on page 4-02000 of the NDA, "the Manufacturing Batch Record Bulk Production Order reflects the amount of xanthan gum and mannitol required for the final product. Actual production requires (of mannitol and xanthan gum). mannitol and xanthan gum used in the manufacturing of drug product batches should be reflected in the master "Production Procedures for representative batch of the Drug Product", for both 0.25% and 0.5% drug products. The master "Production Procedures for representative batch of the Drug Product" should therefore be revised and resubmitted.

Reviewer's Comments:

The applicant has already clarified the discrepancy between the described procedure and the Batch Record. This issue is therefore not related to the safety or efficacy of the product and should not hold up approval.

2. A revised regulatory specifications for the 0.25% and 0.5% drug products should be resubmitted.

Reviewer's Comments:

The regulatory specifications have already been considered acceptable. The need to revised them relates to listing the specifications together on one page instead of in different locations in the NDA. It is therefore not a safety or efficacy issue and should not hold up approval.

3. Please provide representative mock-up labels that will be used on the immediate containers, and representative mock-up cartons that will be used in the packaging of Timolol Maleate Ophthalmic Gel Forming Solution, 0.25% and 0.5%, in fill sizes of 2.5 mL and 5 mL.

Reviewer's Comments:

Consistent with the usual practice for other applications, the Final Printed Labeling including cartons and containers should be requested in the Approval letter.

4. On page 13 of final insert text submitted on 10/13/98, in the storage section of the package insert, the words used are "Store between 2° and 25°C (36° and 77°F) . Protect from light". In the primary container and carton labels of 0.25% and 0.5% products, in the storage section, the words used are "Store at 36°F to 77°F (2°C to 25°C) . Do not freeze. Protect from light". It is recommended that uniform language should be used for stating the storage condition in the package insert, on carton labels and on primary container labels.

Reviewer's Comments:

As identified in the September 29, 1998, submission, there is sufficient information in the NDA to support the deletion of the statement "Do not freeze." This may be submitted with the Final Printed Labeling.

5. Please submit two additional copies of the Methods Validation Packages.

Reviewer's Comments:

Consistent with the usual practice for other applications, the cooperation in completing the Method Validation should be requested in the Approval letter.

**APPEARS THIS WAY
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13 pages
Draft Labeling

Conclusions

1. The submitted studies support the bioequivalence of Timoptic gel forming solution (0.5%) administered once a day and timolol solution (0.5%) administered twice a day.
2. The submitted studies support the bioequivalence of Timoptic gel forming solution formulation (0.25%) administered once a day and timolol solution formulation (0.25%) administered twice a day.

Recommendations

Timolol Maleate Gel Forming Solution, 0.25% and 0.5% (NDA 20-963) is recommended for approval when indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension and open-angle glaucoma



Wiley A. Chambers, M.D.

Medical Officer, Ophthalmology

cc: NDA 20-963
HFD-550/Div Files
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-830/CHEM/Uppoor
HFD-805/MICRO/Stinavage
HFD-880/BIOPHARM/Tandon
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

**APPEARS THIS WAY
ON ORIGINAL**