8.1.5 Study Design

The study design is nearly identical to Study 2, Protocol C-97-71. The major differences were 1) the exclusion of a Xalatan 0.005% treatment arm, 2) the study length was 9 months, and 3) the study was conducted in Europe and Australia.

The primary efficacy variable was mean IOP measured at 9AM, 11AM, and 4PM at Week 2, Month 3, and Month 9, and at 9AM and 11AM at Month 1.5 and Month 6.

Reviewer's Comments:

The primary efficacy variable utilized in the review of this NDA is mean IOP and change in mean IOP from baseline for each time point at Week 2, Month 1.5, Month 3, Month 4.5, Month 6, and Month 9.

Study Medications

• AL-6221 0.0015%	Lot # ASE-2999B; ASE-2970A; ARE-2948B; and 99-500042-3
• AL-6221 0.004%	Lot # ASE-2998B; ASE-2971A; ARE-2946B; 99-500044-3; and 99-500045-3
• AL-6221 Vehicle	Lot # ASE-2996A; ASE-2989; ASE-2972A; ARE-2947A; 98-500002-1; 99-500022-1; and 99-500050-1
• Timoptic 0.5%	Lot # ASE-3003B; ASE-2995; ASE-2977; ASE-2969; ARE-2949; 98-500013-1; 99-500023-1; 99-500031-1; 98-600001-1; 98-600002-1; and 99-500084-1

All masked test medications used during the treatment phase were supplied in a masked DROP-TAINER labeled with the appropriate patient number.

Protocol C-97-79
Study Plan

Activity	Screen	Eligibility Visit 1			Eligibility Visit 2			Week 2 ± 1 day			Month 1.5 ± 3 days		Month 3 ± 3 days			Month 4.5 ± 3 days		Month 6 ± 3 days		Month 9 ± 3 days		
		9 AM	11 AM	4 PM	9 AM	11 AM	4 PM	9 AM	11 AM	4 PM	9 AM	11 AM	9 AM	11 AM	4 PM	9 AM	11 AM	9 AM	11 AM	9 AM	11 AM	4 PM
Screen Patients	X																					
Informed Consent	X																					
Demographics	X																					
Medical History	X																					
Discontinue All Glaucoma Rx	X																					
IOP[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hyperemia Assessment					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Flare/Cells Assessment[b]	X				X			X			X		X			X		X		X		
Visual Acuity (Best corrected) (logMAR scale)	X	X			X			X			X		X			X		X		X		
Biomicroscopy	X	X			X			X			X		X			X		X		X		
Resting Pulse/Blood Pressure	X				X	X		X	X		X	X	X	X		X	X	X	X	X	X	
Dilated Fundus	X																				X	
Automated Perimetry	X[c]																				X[f]	
Gonioscopy[d]	X																					
Iris/eyelash photographs					X						X		X			X		X		X		
Dispense study meds[e]							X			X		X			X		X		X			
Adverse Events								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Rx																				X		
Exit Patient																						X

[a]IOP measurements had to be be within ± 30 minutes of the required time.
[b]Flare/cells were assessed at all sites according to the grading provided in the Manual of Definitions.
[c]Automated Perimetry, if not performed at Screening, could have been performed between Screening and Eligibility 1 Visit. Visual fields were to be faxed to Alcon and approved prior to drug dispensing.
[d]Gonioscopy was to be conducted only if this procedure had not been performed and documented within the last six (6) months.
[e]Dispensation of medications as needed.

Disposition and Demographics

All 573 randomized subjects received treatment and 524 subjects completed the study.

Subject Disposition

	Number of Subjects			
	AL-6221 0.0015%	AL-6221 0.004%	AL-6221 Vehicle	Total
Randomized	190	197	186	573
Discontinued prematurely	12	19	18	49
Included in safety evaluations	190	197	186	573
Included in intent-to-treat analysis	190	197	185	572
Included in per protocol analysis	168	176	163	507

Reviewer's Comments:

The intent-to-treat population excluded one subject who received treatment but had no on-treatment visit data.

Summary of Reasons for Premature Discontinuation from Study

Reason For Discontinuation	Treatment Group			
	AL6221 0.0015%	AL6221 0.004%	Timoptic 0.5%	Total
Adverse Event	8	11	8	27
Inadequate Control of IOP	3	2	5	10
Patient Decision	0	3	0	3
Lost to Follow-up	0	0	2	2
Noncompliance	0	1	2	3
Inclusion Criteria – menopausal status	1	2	0	3
Patient Moved	0	0	1	1
Total	**12**	**19**	**18**	**49**

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Duration (Days)	Reason
766	2802	Timoptic 0.5%	59	Adverse event-cough increase, chest pain
	2806	AL-6221 0.0015%	91	Adverse event-peptic ulcer
	2823	AL-6221 0.0015%	92	Inadequate control of IOP
906	2119	AL-6221 0.0015%	167	Women not post-menopausal
1487	104	AL-6221 0.004%	168	Adverse event-skin discoloration, hair disorder
1696	6505	AL-6221 0.004%	47	Inadequate control of IOP
	6509	Timoptic 0.5%	166	Adverse event-carcinoma
1714	2902	Timoptic 0.5%	154	Adverse event-carcinoma
1732	303	AL-6221 0.004%	273	Adverse event-hemiplegia, cerebrovascular accident
1792	502	Timoptic 0.5%	250	Lost to F/U
1820	3209	AL-6221 0.004%	74	Adverse event-hyperemia eye
	3218	AL-6221 0.004%	42	Subject decision unrelated to an adverse event
1824	1701	AL-6221 0.0015%	199	Adverse event-cerebral thrombosis
1829	2007	AL-6221 0.004%	255	Non-compliance
1833	3702	AL-6221 0.004%	98	Pt of chidbearing potential
	3703	Timoptic 0.5%	101	Inadequate control of IOP
	3704	AL-6221 0.0015%	15	Inadequate control of IOP
	3707	Timoptic 0.5%	49	Inadequate control of IOP
1836	7007	Timoptic 0.5%	44	Inadequate control of IOP
1841	2301	AL-6221 0.0015%	69	Adverse event-dizziness
	2305	AL-6221 0.004%	77	Adverse event-dry eye
	2306	AL-6221 0.0015%	20	Adverse event-hyperemia eye, eye fatigue, abnormal accomodation
	2308	AL-6221 0.0015%	98	Adverse event-hyperemia eye, follicles conjunctivitis
1897	3402	Timoptic 0.5%	264	Adverse event-neoplasm, surgical/medical proc
1898	712	Timoptic 0.5%	273	Pt moved to Kosovo
1984	2203	AL-6221 0.004%	143	Adverse event-hyperemia eye
2025	2403	Timoptic 0.5%	84	Adverse event-carcinoma
2041	5503	Timoptic 0.5%	273	Adverse event-hypotension, cerebral ischemia, asthenia
2042	5204	Timoptic 0.5%	194	Non-compliance
2104	3303	Timoptic 0.5%	77	Inadequate control of IOP
2144	4305	AL-6221 0.004%	110	Adverse event-lung disorder
	4307	AL-6221 0.0015%	45	Adverse event-weight increase, dyspnea, peripheral edema, heart failure, skin discoloration
2312	407	AL-6221 0.004%	18	Adverse event-headache, browache
2343	4710	AL-6221 0.004%	177	Pt of childbearing potential
2350	4203	Timoptic 0.5%	133	Non-compliance
	4211	AL-6221 0.004%	42	Adverse event-pruritus eye
2352	4102	AL-6221 0.004%	86	Inadequate control of IOP
	4103	Timoptic 0.5%	129	Adverse event-discomfort eye
2409	5107	AL-6221 0.004%	49	Subject decision unrelated to an adverse event
2411	5803	Timoptic 0.5%	77	Adverse event-asthma
	5809	AL-6221 0.004%	14	Adverse event-discomfort eye
2412	4908	AL-6221 0.0015%	60	Adverse event-hyperemia eye, conjunctivitis
	4911	AL-6221 0.0015%	191	Inadequate control of IOP
	4912	AL-6221 0.004%	14	Subject decision unrelated to an adverse event
	4913	Timoptic 0.5%	440	Lost to F/U
2419	5602	AL-6221 0.004%	143	Adverse event-discomfort eye, hyperemia eye, pruritus eye
2425	4803	AL-6221 0.004%	272	Adverse event-discomfort eye, hyperemia eye
	4805	Timoptic 0.5%	57	Inadequate control of IOP
	4806	AL-6221 0.0015%	31	Adverse event-hyperemia eye, discomfort eye, erythema, pruritus

Summary of Demographic Characteristics (Intent-to-Treat)

Treatment	Age Mean[a]	Std	N	Min	Max
AL-6221 0.0015%	64.5	9.9	190	34	88
AL-6221 0.004%	63.0	10.3	197	31	87
Timoptic 0.5%	62.5	10.6	185	36	86

[a] p=0.163 for test of mean age differences among groups.

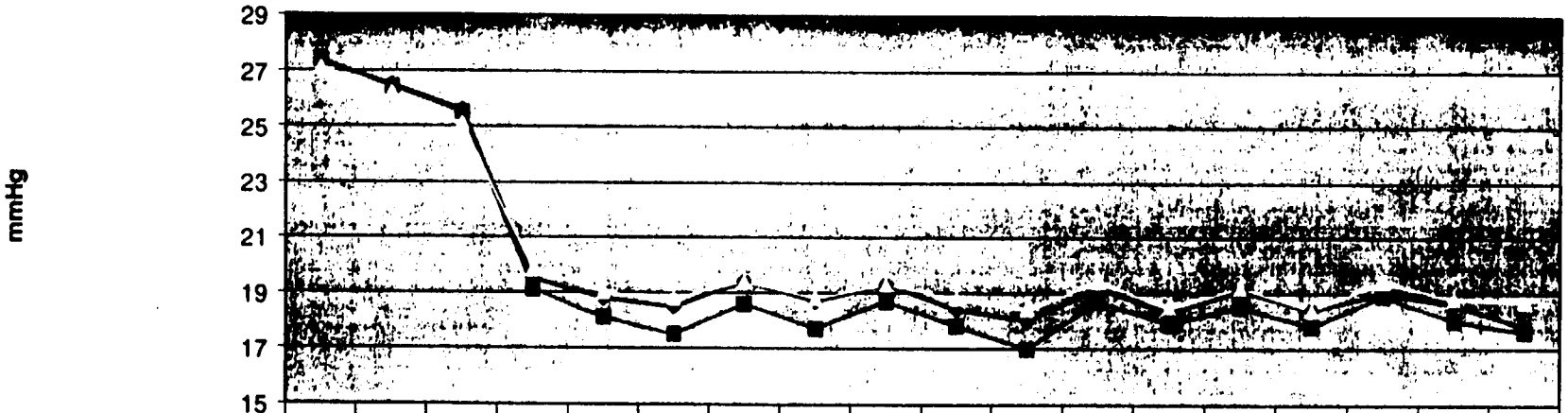
	Treatment: AL-6221 0.0015% N	%	AL-6221 0.004% N	%	Timoptic 0.5% N	%	P-value
Age Group							
<65	92	48.4	106	53.8	98	53.0	0.525
>=65	98	51.6	91	46.2	87	47.0	
<65	92	48.4	106	53.8	98	53.0	0.919
>=65-<75	70	36.8	68	34.5	66	35.7	
>=75-<85	26	13.7	22	11.2	20	10.8	
>=85-<95	2	1.1	1	0.5	1	0.5	
Sex							
MALE	92	48.4	96	48.7	96	51.9	0.758
FEMALE	98	51.6	101	51.3	89	48.1	
Race							
CAUCASIAN	185	97.4	194	98.5	181	97.8	0.902
BLACK	3	1.6	2	1.0	2	1.1	
ASIAN	1	0.5	1	0.5	2	1.1	
OTHER	1	0.5	--	--	--	--	
Iris Color							
BROWN	59	31.1	70	35.5	59	31.9	0.849
HAZEL	31	16.3	24	12.2	23	12.4	
GREEN	15	7.9	12	6.1	13	7.0	
BLUE	69	36.3	79	40.1	74	40.0	
GREY	16	8.4	12	6.1	16	8.6	
Diagnosis (ICD9)							
OCULAR HYPERTENSION	74	38.9	74	37.6	73	39.5	0.930
OPEN-ANGLE GLAUCOMA	105	55.3	109	55.3	99	53.5	
PIGMENTARY GLAUCOMA	4	2.1	3	1.5	2	1.1	
PSEUDOEXFOLIATION GLAUCOMA	7	3.7	11	5.6	11	5.9	

APPEARS THIS WAY
ON ORIGINAL

8.1.5 Efficacy – Protocol C-97-99 Intent-to-Treat Population

Primary Efficacy Variable

Mean IOP per Visit and Time

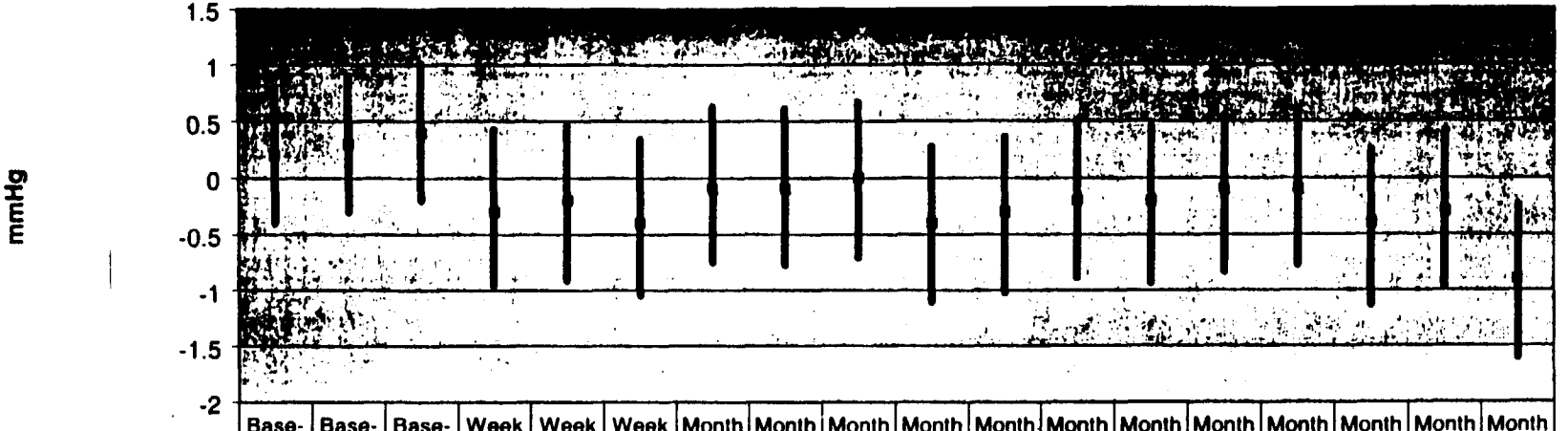


	Base-line 9AM	Base-line 11AM	Base-line 4PM	Week 2 9AM	Week 2 11AM	Week 2 4PM	Month 1.5 9AM	Month 1.5 11AM	Month 3 9AM	Month 3 11AM	Month 3 4PM	Month 4.5 9AM	Month 4.5 11AM	Month 6 9AM	Month 6 11AM	Month 9 9AM	Month 9 11AM	Month 9 4PM
AL-6221 0.0015%	27.3	26.5	25.6	19.5	18.8	18.5	19.4	18.7	19.3	18.4	18	19.2	18.3	19.1	18.4	19	18.6	17.8
AL-6221 0.004%	27.4	26.4	25.5	19.1	18.1	17.5	18.6	17.7	18.7	17.8	17	18.7	17.9	18.5	17.8	18.9	18	17.6
Timoptic 0.5%	27.1	26.2	25.1	19.8	19	18.8	19.4	18.8	19.3	18.8	18.4	19.4	18.5	19.2	18.4	19.4	18.8	18.7

Reviewer's Comments: *Baseline mean IOP of the three treatment arms is similar. The mean IOP of AL-6221 0.0015% dosed QPM, AL-6221 0.004% dosed QPM, and Timoptic 0.5% dosed BID demonstrate similar ability to lower IOP over visit days and time.*

APPEARS THIS WAY
ON ORIGINAL

Mean Difference (AL-6221 0.0015% - Timoptic 0.5%) with 95% Confidence Intervals

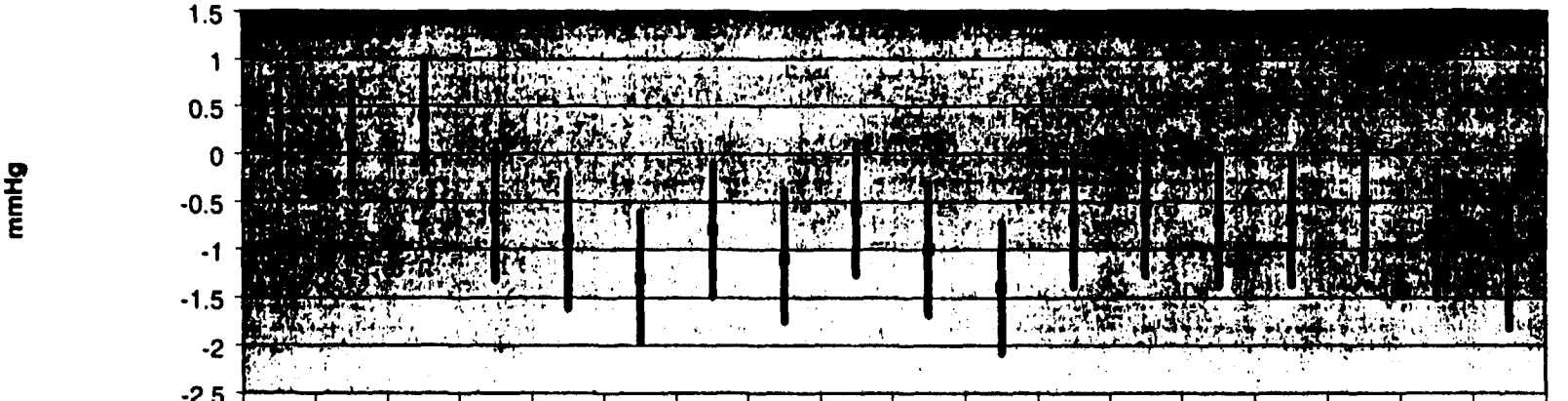


	Base-line 9AM	Base-line 11AM	Base-line 4PM	Week 2 9AM	Week 2 11AM	Week 2 4PM	Month 1.5 9AM	Month 1.5 11AM	Month 3 9AM	Month 3 11AM	Month 3 4PM	Month 4.5 9AM	Month 4.5 11AM	Month 6 9AM	Month 6 11AM	Month 9 9AM	Month 9 11AM	Month 9 4PM
Lower CI	-0.4	-0.3	-0.2	-0.95	-0.91	-1.04	-0.75	-0.77	-0.71	-1.1	-1.02	-0.88	-0.93	-0.83	-0.77	-1.13	-0.97	-1.61
Upper CI	0.8	0.9	1	0.42	0.46	0.33	0.62	0.6	0.66	0.27	0.35	0.49	0.45	0.54	0.61	0.24	0.4	-0.24
■ Mean Difference	0.2	0.3	0.4	-0.3	-0.2	-0.4	-0.1	-0.1	0	-0.4	-0.3	-0.2	-0.2	-0.1	-0.1	-0.4	-0.3	-0.9

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.0015% and Timoptic 0.5% is not statistically significant at almost all time points and ranges from 0 to –0.9 mmHg. The 95% confidence interval crosses zero at all time points measured except Month 9 4PM. The IOP lowering ability of AL-6221 0.0015% is not superior to Timoptic 0.5% by a clinically significant amount.*

APPEARS THIS WAY
ON ORIGINAL

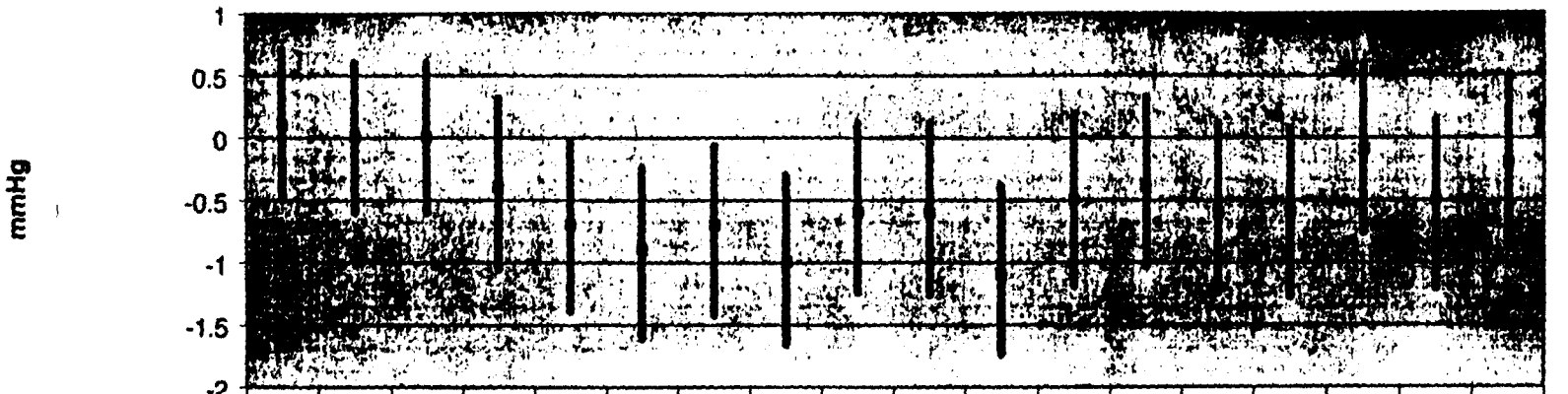
Mean Difference (AL-6221 0.004% - Timoptic 0.5%) with 95% Confidence Intervals



	Base-line 9AM	Base-line 11AM	Base-line 4PM	Week 2 9AM	Week 2 11AM	Week 2 4PM	Month 1.5 9AM	Month 1.5 11AM	Month 3 9AM	Month 3 11AM	Month 3 4PM	Month 4.5 9AM	Month 4.5 11AM	Month 6 9AM	Month 6 11AM	Month 9 9AM	Month 9 11AM	Month 9 4PM
Lower CI	-0.3	-0.4	-0.2	-1.32	-1.62	-1.97	-1.49	-1.75	-1.27	-1.68	-2.08	-1.38	-1.27	-1.38	-1.37	-1.2	-1.5	-1.82
Upper CI	0.9	0.8	1	0.04	-0.26	-0.61	-0.13	-0.39	0.09	-0.32	-0.72	-0.02	0.09	-0.02	-0.01	0.16	-0.14	-0.46
■ Mean Difference	0.3	0.2	0.4	-0.6	-0.9	-1.3	-0.8	-1.1	-0.6	-1	-1.4	-0.7	-0.6	-0.7	-0.7	-0.5	-0.8	-1.1

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.004% and Timoptic 0.5% is statistically significant at a majority of the time points measured and ranges from –0.5 to –1.4 mmHg. The 95% confidence interval crosses zero at Week 2 9AM, Month 3 9AM, Month 4.5 11AM, and Month 9 9AM. The IOP lowering ability of AL-6221 0.004% is not superior to Timoptic 0.5% by a clinically significant amount.*

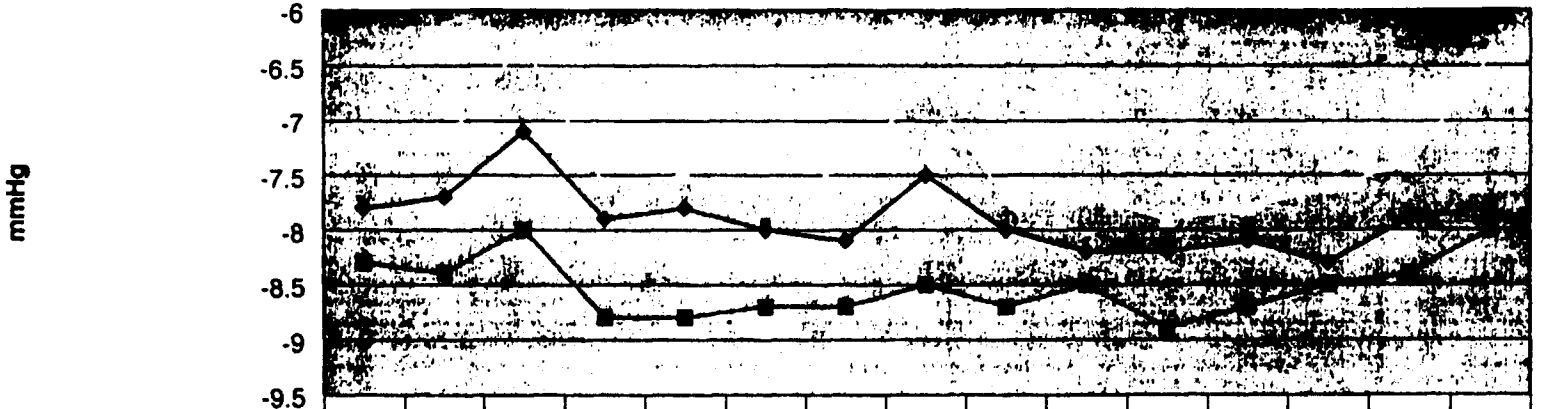
Mean Difference (AL-6221 0.004% - AL-6221 0.0015%) with 95% Confidence Intervals



	Base-line 9AM	Base-line 11AM	Base-line 4PM	Week 2 9AM	Week 2 11AM	Week 2 4PM	Month 1.5 9AM	Month 1.5 11AM	Month 3 9AM	Month 3 11AM	Month 3 4PM	Month 4.5 9AM	Month 4.5 11AM	Month 6 9AM	Month 6 11AM	Month 9 9AM	Month 9 11AM	Month 9 4PM
Lower CI	-0.5	-0.6	-0.6	-1.05	-1.39	-1.61	-1.42	-1.66	-1.24	-1.26	-1.74	-1.19	-1.03	-1.24	-1.28	-0.76	-1.21	-0.89
Upper CI	0.7	0.6	0.6	0.3	-0.04	-0.25	-0.07	-0.31	0.11	0.09	-0.39	0.17	0.32	0.11	0.07	0.59	0.14	0.47
■ Mean Difference	0.1	0	0	-0.4	-0.7	-0.9	-0.7	-1	-0.6	-0.6	-1.1	-0.5	-0.4	-0.6	-0.6	-0.1	-0.5	-0.2

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.0015% and AL-6221 0.004% is not statistically significant at a majority of the time points measured and ranges from –0.1 to –1.1 mmHg. The difference in the IOP lowering ability of AL-6221 0.0015% and AL-6221 0.004% is not clinically significant.*

Change in Mean IOP from Baseline per Visit and Time



	Week 2 9AM	Week 2 11AM	Week 2 4PM	Month 1.5 9AM	Month 1.5 11AM	Month 3 9AM	Month 3 11AM	Month 3 4PM	Month 4.5 9AM	Month 4.5 11AM	Month 6 9AM	Month 6 11AM	Month 9 9AM	Month 9 11AM	Month 9 4PM
AL-6221 0.0015%	-7.8	-7.7	-7.1	-7.9	-7.8	-8	-8.1	-7.5	-8	-8.2	-8.2	-8.1	-8.3	-7.9	-7.8
AL-6221 0.004%	-8.3	-8.4	-8	-8.8	-8.8	-8.7	-8.7	-8.5	-8.7	-8.5	-8.9	-8.7	-8.5	-8.4	-8
Timoptic 0.5%	-7.3	-7.2	-6.3	-7.6	-7.5	-7.8	-7.4	-6.7	-7.7	-7.7	-7.9	-7.8	-7.6	-7.4	-6.4

Reviewer's Comments: *When corrected for baseline, the change in mean IOP from baseline ranges from –7.1 to –8.3 mmHg for AL-6221 0.0015%, from –8.0 to –8.9 mmHg for AL-6221 0.004%, and from –6.3 to –7.9 mm Hg for Timoptic 0.5%.*

APPEARS THIS WAY
ON ORIGINAL

8.1.5 Safety

Adverse Events

Serious adverse events other than death were reported for 6/190 (3.2%) subjects treated with AL-6221 0.0015%, 7/197 (3.6%) subjects treated with AL-6221 0.004%, and 10/186 (5.4%) subjects treated with Timoptic 0.5%. These other serious adverse events resulted in the premature discontinuation from the study for one subject treated with AL-6221 0.0015%, two subjects treated with AL-6221 0.004%, and one subject treated with Timoptic 0.5%.

Other Serious Adverse Events

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
2144	4306	AL-6221 0.0015%	Dyspnea	Continuing w/Tx	No
			Bone Disorder	Continuing w/Tx	No
			Pulmonary Embolus	Resolved w/Tx	No
			Pain Chest	Continuing w/Tx	No
			Infection	Resolved w/Tx	No
2412	4911	AL-6221 0.0015%	Dyspnea	Resolved w/Tx	No
2457	6007	AL-6221 0.0015%	Pneumonia	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
1824	1701	AL-6221 0.0015%	Cerebral Thrombosis	Continuing w/Tx	Yes
1696	6501	AL-6221 0.0015%	Infection	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
2476	6207	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
2144	4305	AL-6221 0.004%	Lung Disorder	Resolved w/Tx	Yes
			Arrhythmia	Resolved w/Tx	No
1732	303	AL-6221 0.004%	Hemiplegia	Continuing w/Tx	Yes
			Cerebrovascular Accident	Resolved w/Tx	Yes
1696	6502	AL-6221 0.004%	Anomaly Congenital MS	Resolved w/Tx	No
			Surgical/Medical Proc	Resolve w/Tx	No
1717	3103	AL-6221 0.004%	GI Disorder	Resolved wo/Tx	No
1820	3219	AL-6221 0.004%	Cardiovascular Disorder	Resolve w/Tx	No
2042	5208	AL-6221 0.004%	Cerebral Ischemia	Resolved w/Tx	No
1714	2905	AL-6221 0.004%	Infection	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2144	4304	Timoptic 0.5%	Urogenital Disorder	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
1829	2009	Timoptic 0.5%	Colitis	Resolved w/Tx	No
1715	3009	Timoptic 0.5%	Gastritis	Resolved w/Tx	No
			Pain Abdomen	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2476	6208	Timoptic 0.5%	Hepatitis	Resolved w/Tx	No
2041	5503	Timoptic 0.5%	Hypotension	Continuing w/Tx	Yes
			Cerebral Ischemia	Continuing w/Tx	Yes
			Asthenia	Continuing w/Tx	Yes
2156	2508	Timoptic 0.5%	Surgical/Medical Proc	Resolved w/Tx	No
1729	3805	Timoptic 0.5%	Surgical/Medical Proc	Resolved w/Tx	No
1696	6509	Timoptic 0.5%	Surgical/Medical Proc	Resolved wo/Tx	No
2594	7209	Timoptic 0.5%	Surgical/medical Proc	Resolved w/Tx	No

D/C Pt = Discontinued Patient

Fatal Serious Adverse Events

Investigator Number	Patient Number	Treatment	Duration (Days)	Coded Adverse Event
2025	2403	Timoptic 0.5%	111	Carcinoma
1714	2902	Timoptic 0.5%	194	Carcinoma
1696	6509	Timoptic 0.5%	183	Carcinoma
1897	3402	Timoptic 0.5%	234	Neoplasm Surgical/Medical Proc

Eight subjects (4.2%) receiving AL-6221 0.0015%, eleven subjects (5.6%) receiving AL-6221 0.004%, and eight subjects (4.3%) receiving Timoptic 0.5% discontinued from the study due to adverse events.

Frequency and Incidence of ocular and Non-ocular Adverse Events
Occurring at Rates Greater than 1%

Coded Adverse Event	AL-6221 0.0015% N=190	AL-6221 0.004% N=197	Timoptic 0.5% N=186
	N (%)	N (%)	N (%)
All Events	114 (60.0%)	133 (67.5%)	88 (47.3)
OCULAR			
Hyperemia Eye	50 (26.3)	69 (35.0)	15 (8.1)
Discomfort Eye	15 (7.9)	14 (7.1)	7 (3.8)
Pruritus Eye	7 (3.7)	15 (7.6)	3 (1.6)
Iris Discolor	10 (5.3)	7 (3.6)	
Visual Acuity Decrease	2 (1.1)		7 (3.8)
Cataract Nos	3 (1.6)	3 (1.5)	3 (1.6)
Foreign Body Sensation	5 (2.6)	3 (1.5)	
Vision Blurred	3 (1.6)		3 (1.6)
Dry Eye	3 (1.6)	4 (2.0)	
Pain Eye	3 (1.6)	4 (2.0)	
Conjunctivitis	2 (1.1)	3 (1.5)	2 (1.1)
Cataract			2 (1.1)
Optic Nerve Disease		4 (2.0)	
Blepharitis	3 (1.6)		
Inflammatory Cells Aqueous	3 (1.6)		2 (1.1)
Aqueous Flare	2 (1.1)		
Surgical/Medical Proc	2 (1.1)		
Retinal Disease	3 (1.6)		
Hair Disease		3 (1.5)	
Lid Disease			2 (1.1)
Meibomitis		3 (1.5)	
Tearing			2 (1.1)
Visual Field Defect			2 (1.1)
NON-OCULAR			
Body As A Whole			
Surgical/Medical Proc	7 (3.7)	7 (3.6)	9 (4.8)
Flu Syndrome	5 (2.6)	14 (7.1)	4 (2.2)
Infection	6 (3.2)	5 (2.5)	5 (2.7)
Headache	3 (1.6)	9 (4.6)	

Coded Adverse Event	AL-6221 0.0015% N=190	AL-6221 0.004% N=197	Timoptic 0.5% N=186
	N (%)	N (%)	N (%)
Pain	4 (2.1)	4 (2.0)	5 (2.7)
Injury Accidental	3 (1.6)		5 (2.7)
Cold Syndrome	3 (1.6)		3 (1.6)
Pain Back	4 (2.1)		2 (1.1)
Asthenia	2 (1.1)		4 (2.2)
Pain Chest	2 (1.1)		2 (1.1)
Pain Abdomen	3 (1.6)		2 (1.1)
Allergy	3 (1.6)		
Carcinoma			3 (1.6)
Cardiovascular System			
Hypertension	9 (4.7)	11 (5.6)	12 (6.5)
Angina Pectoris	2 (1.1)		
Digestive System			
Colitis			2 (1.1)
Diarrhea	2 (1.1)		
GI Disease		4 (2.0)	6 (3.2)
Endocrine System			
Diabetes Mellitus	2 (1.1)		2 (1.1)
Hypothyroidism			2 (1.1)
Metabolic and Nutrition			
Hypercholesterolemia	4 (2.1)		3 (1.6)
Musculo-Skeletal System			
Arthrosis	3 (1.6)		
Arthritis	2 (1.1)		
Myalgia	2 (1.1)		
Arthritis Rheumatoid	2 (1.1)		
Nervous System			
Dizziness	7 (3.7)		
Depression			2 (1.1)
Anxiety	2 (1.1)		
Vertigo	2 (1.1)		
Respiratory System			
Rhinitis	4 (2.1)	3 (1.5)	3 (1.6)
Bronchitis	5 (2.6)		3 (1.6)
Dyspnea	3 (1.6)		
Sinusitis	2 (1.1)		3 (1.6)
Pharyngitis			5 (2.7)
Asthma			2 (1.1)
Cough Increase			2 (1.1)
Skin And Appendages			
Dermatitis		3 (1.5)	
Pruritus	2 (1.1)		
Herpes Zoster	2 (1.1)		
Urogenital System			
Cystitis	3 (1.6)		
Menopause		4 (2.0)	

Ocular Hyperemia

A statistically significant difference in ocular hyperemia among the treatment groups was observed (p=0.001). A concentration related increase in mean ocular hyperemia was observed between AL-6221 0.0015% and Al-6221 0.004% compared to Timoptic 0.5%.

Frequency and Incidence of Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015%	190	49	25.8
AL-6221 0.004%	197	65	32.5
Timoptic 0.5%	186	13	7.0

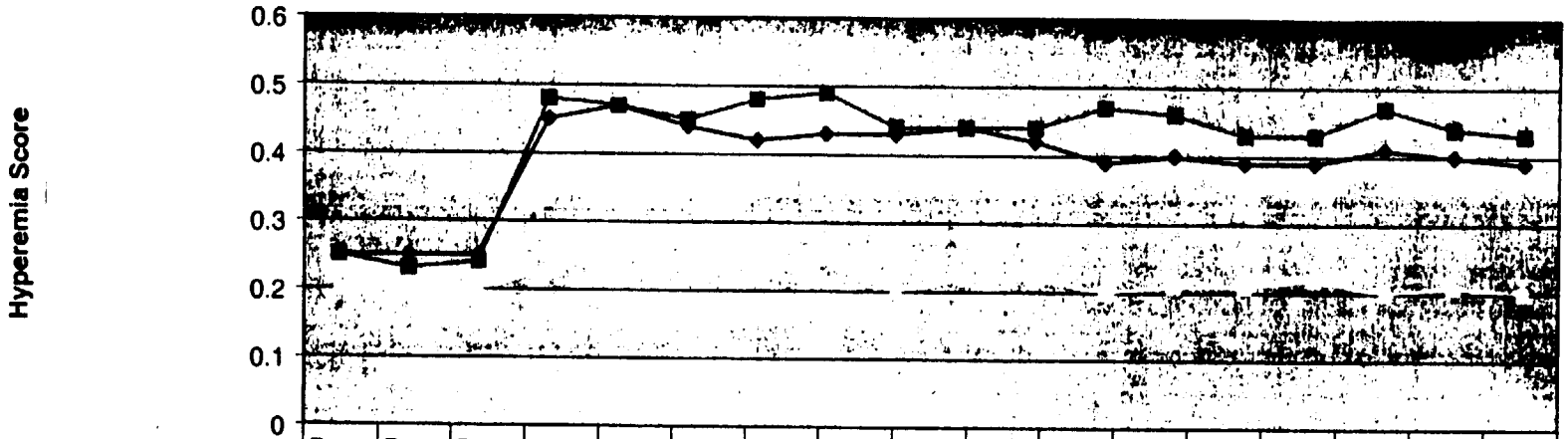
Patient 502 (Timoptic 0.5%) had no follow-up data.

Frequency and Incidence of Discontinued Patients Due to Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015%	190	4	2.1
AL-6221 0.004%	197	4	2.0
Timoptic 0.5%	186	0	0

Patient 502 (Timoptic 0.5%) had no follow-up data.

Mean Hyperemia Score per Visit Day and Time



	Base-line 9AM	Base-line 11AM	Base-line 4PM	Week 2 9AM	Week 2 11AM	Week 2 4PM	Month 1.5 9AM	Month 1.5 11AM	Month 3 9AM	Month 3 4PM	Month 4.5 9AM	Month 4.5 11AM	Month 6 9AM	Month 6 11AM	Month 9 9AM	Month 9 11AM	Month 9 4PM
AL-6221 0.0015%	0.25	0.25	0.25	0.45	0.47	0.44	0.42	0.43	0.43	0.42	0.39	0.4	0.39	0.39	0.41	0.4	0.39
AL-6221 0.004%	0.25	0.23	0.24	0.48	0.47	0.45	0.48	0.49	0.44	0.44	0.47	0.46	0.43	0.43	0.47	0.44	0.43
Timoptic 0.5%	0.2	0.2	0.2	0.23	0.25	0.23	0.22	0.25	0.2	0.22	0.2	0.21	0.21	0.22	0.2	0.21	0.2

Reviewer's Comments: *Baseline mean hyperemia score for the three treatment arms is similar. The mean hyperemia score for AL-6221 0.0015% and AL-6221 0.004% dosed QPM is consistently higher than for Timoptic 0.5% dosed BID. A concentration related increase in mean hyperemia score is associated with AL-6221.*

Visual Acuity

No statistically significant difference in visual acuity change from baseline to final visit (p=0.674) or from baseline to worst visit (p=0.133) was observed among treatment groups.

Change in Visual Acuity (logMAR) from Baseline to Final Visit

	Treatment Group			
Line Changes	AL-6221 0.0015% N (%)	AL-6221 0.004% N (%)	Timoptic 0.5% N (%)	Total N (%)
N	190	197	185	572
≥ 2 lines loss	6 (3.2)	7 (3.6)	12 (6.5)	25 (4.4)
1 line loss	36 (18.9)	39 (19.8)	29 (15.7)	104 (18.2)
No Change	132 (69.5)	142 (72.1)	132 (71.4)	406 (71.0)
1 line gain	13 (6.8)	7 (3.6)	10 (5.4)	30 (5.2)
≥ 2 lines gain	3 (1.6)	2 (1.0)	2 (1.1)	7 (1.2)

Patient 502 (timoptic 0.5%) had no follow-up data.

Change in Visual Acuity (logMAR) from Baseline to Worse Visit

	Treatment Group			
Line Changes	AL-6221 0.0015% N (%)	AL-6221 0.004% N (%)	Timoptic 0.5% N (%)	Total N (%)
N	190	197	185	572
≥ 2 lines loss	32 (16.8)	41 (20.8)	44 (23.8)	117 (20.5)
1 line loss	71 (37.4)	80 (40.6)	68 (36.8)	219 (38.3)
No Change	82 (43.2)	74 (37.6)	73 (39.5)	229 (40.0)
1 line gain	4 (2.1)	0 (0)	0 (0)	4 (0.7)
≥ 2 lines gain	1 (0.5)	2 (1.0)	0 (0)	3 (0.5)

Patient 502 (Timoptic 0.5%) had no follow-up data.

Iris Pigmentation Change

Iris photographs of each eye were taken at Eligibility 2 9AM (baseline), Month 1.5, Month3, Month 4.5, Month 6, and Month 9.

A statistically significant difference in iris pigmentation change was noted among treatment groups beginning at Month 6 (p=0.026).

Patients with Iris Pigmentation Change

Treatment	%	N	Total
AL-6221 0.0015% with Vehicle	4.7	9	190
AL-6221 0.004% with Vehicle	3.6	7	193
Timoptic 0.5%	0.0	0	185

p=0.005 from Fisher's Exact test for treatment group comparison.
Patients 3218, 4912, 5107, 5809 (AL-6221 0.004%) and 502 (Timoptic 0.5%) had no follow-up data.

Percent of Patients with Iris Pigmentation Change by Visit

		MON1.5 9AM	MON 3 9AM	MON 4.5 9AM	MON 6 9AM	MON 9 9AM	EARLY EXIT
AL-6221 0.0015% with Vehicle	%	0.6	0.6	2.3	4.1	5.1	0.0
	N	1	1	4	7	9	0
	Total	178	178	173	172	175	12
AL-6221 0.004% with Vehicle	%	0.0	0.6	1.2	2.8	4.0	0.0
	N	0	1	2	5	7	0
	Total	183	179	173	178	177	15
Timoptic 0.5%	%	0.0	0.0	0.0	0.0	0.0	0.0
	N	0	0	0	0	0	0
	Total	167	172	166	165	167	17

p=0.653 (month 1.5), 1.000 (month 3), 0.174 (month 4.5), 0.026 (month 6), and 0.005 (month 9) from Fisher's Exact test for treatment group comparison.

Reviewer's Comments:

Iris Pigmentation change is consistent with an ocularly administered prostaglandin-type effect. A change is detected as early as 1.5 months following initiation of therapy for the group treated with AL-6221 0.0015% and beginning Month 3 for the group treated with AL-6221 0.004%. The prevalence increases with duration of therapy for both treatment groups.

Eyelashes

Eyelash photographs of each eye were taken at Eligibility 2 9AM (baseline), Month 1.5, Month 3, Month 4.5, Month 6, and Month 9.

A statistically significant (p=0.001) difference was observed among treatment groups beginning Month 3 of the study.

Percent of Subjects with Eyelash Change by Category

Treatment	Total N	Change Reported		Color Change		Length Change		Density Change		Thickness Change	
	N	N	%	N	%	N	%	N	%	N	%
AL-6221 0.0015% with Vehicle	190	123	64.7	96	50.5	123	64.7	114	60.0	81	42.6
AL-6221 0.004% with Vehicle	193	147	76.2	112	58.0	146	75.6	140	72.5	113	58.5
Timoptic 0.5%	185	6	3.2	4	2.2	6	3.2	5	2.7	0	0.0

p<0.001 (all changes) from chi-square test for treatment group comparison.
Patients 3218, 4912, 5107, 5809 (AL-6221 0.004%) and 502 (Timoptic 0.5%) had no follow-up data.

Percent of Subjects with Eyelash Change by Visit

		MON1.5 9AM	MON 3 9AM	MON 4.5 9AM	MON 6 9AM	MON 9 9AM	EARLY EXIT
AL-6221 0.0015% with Vehicle	%	1.7	43.6	58.0	60.1	67.4	25.0
	N	3	78	101	104	118	3
	Total	178	179	174	173	175	12
AL-6221 0.004% with Vehicle	%	1.6	59.3	66.7	71.2	76.8	60.0
	N	3	108	118	126	136	9
	Total	183	182	177	177	177	15
Timoptic 0.5%	%	0.0	0.0	1.8	2.4	3.0	0.0
	N	0	0	3	4	5	0
	Total	167	172	167	165	167	17

p=0.257 (month 1.5) and p<.001 (all other visits) from Fisher's Exact test for treatment group comparison.

Reviewer's Comments:

A concentration related change in eyelash color, length, density, and thickness is consistent with an ocularly administered prostaglandin-type effect. The prevalence of eyelash change increases with duration of therapy. Whether these changes are purely cosmetic or have safety issues have not been determined.

Aqueous Flare and Inflammatory Cells

No clinically or statistically significant difference in increase of ocular flare (p=0.548) or inflammatory cells (p=0.401) was observed among treatment groups.

Cup/Disc Ratio

No clinically or statistically significant difference (p=0.287) in increase of cup/disc ratio was observed among treatment groups.

Reviewer's Comments:

Nineteen subjects, three receiving AL-6221 0.0015%, five receiving AL-6221 0.004%, and eleven receiving Timoptic 0.5% had missing follow-up data.

Visual Field

For subjects evaluated with the [redacted] there was a trend towards statistical significance observed among the treatment groups in the change in mean deviation from Screening to Exit Visits (p=0.084). There was a statistical significant difference between the groups treated with AL-6221 0.0015% and Timoptic 0.5% (p=0.0285). No statistically significant difference (p=0.606) in corrected pattern standard deviation among treatment groups was observed.

For subjects evaluated with the [redacted] no statistically significant difference in mean defect (p=0.442) or corrected loss variance change (p=0.632) was observed among treatment groups.

Ocular Signs

No statistically significant (p=0.323 to 0.914) difference in worsening of ocular signs (cornea, iris/anterior chamber, lens, and vitreous) was observed among treatment groups.

Dilated Fundus Examination

No statistically significant difference in fundus parameters of retina/macula/choroid (p=0.168), optic nerve (p=0.655), or disc pallor (p=0.099) was observed among treatment groups.

Vital Signs

A statistically significant change in pulse from baseline was observed among treatment groups (p<0.001).

No statistically significant difference in systolic blood pressure (p=0.54) and diastolic blood pressure (p=0.598) was observed among treatment groups.

Pulse Change from Baseline (Beats per Minute)

Treatment		Change from Baseline												
		E2 11AM	W2 9AM	W2 11AM	M 1.5 9AM	M 1.5 11AM	M 3 9AM	M 3 11AM	M 4.5 9AM	M 4.5 11AM	M 6 9AM	M 6 11AM	M 9 9AM	M 9 11AM
AL-6221	Mean	74.2	1.5	0.4	1.6	0.1	1.8	0.3	1.0	-1.1	0.4	0.0	0.9	-0.8
0.0015% +	Std	10.4	9.4	9.3	9.1	8.3	9.0	9.1	9.1	8.8	8.6	9.2	8.5	9.0
Vehicle	N	184	183	183	178	176	177	177	174	171	172	173	171	171
	Min	50	-60	-72	-27	-26	-22	-26	-24	-22	-24	-26	-18	-21
	Max	132	32	23	27	27	29	32	28	24	28	25	24	27
AL-6221	Mean	72.1	0.3	-0.4	0.3	-0.5	-0.9	-1.2	-0.0	-1.4	-0.0	-1.5	-0.1	-0.2
0.004% +	Std	10.3	8.1	7.1	8.6	9.0	8.8	8.3	8.7	8.6	9.3	9.0	9.9	9.8
Vehicle	N	194	191	190	190	189	183	182	179	178	178	178	173	174
	Min	47	-30	-22	-29	-29	-30	-30	-20	-28	-30	-26	-32	-34
	Max	110	34	21	24	28	30	28	26	20	24	26	36	34
Timoptic	Mean	73.1	-2.4	-3.8	-3.0	-4.4	-1.4	-2.8	-2.6	-4.1	-3.1	-4.8	-2.9	-3.3
0.5%	Std	10.0	9.4	9.4	9.8	9.7	9.8	9.8	10.8	10.1	10.1	9.8	9.9	9.9
	N	184	182	179	180	175	175	172	173	169	167	167	165	162
	Min	48	-34	-35	-36	-40	-30	-32	-44	-40	-44	-46	-40	-44
	Max	112	28	15	24	24	36	20	23	21	18	16	23	24

p<0.001 from analysis of variance for treatment group comparison of change from baseline.
E = Eligibility. W = Week. M = Month.

Clinical Laboratory Evaluation

No laboratory evaluations were performed.

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8.1.5 Reviewer's Summary of Efficacy and Safety

AL-6221 0.0015% dosed once daily in the evening and AL-6221 0.004% dosed once daily in the evening, demonstrate efficacy in the ability to lower IOP. The change in mean IOP from baseline ranges from –7.1 to –8.3 mmHg for AL-6221 0.0015%, from –8.0 to –8.9 mmHg for AL-6221 0.004%, and from –6.3 to –7.9 mmHg for Timoptic 0.5%.

The IOP lowering ability of AL-6221 0.0015% and AL-6221 0.004% is not superior to Timoptic 0.5% by a clinically significant amount.

The difference in the IOP ability of the two concentrations of AL-6221 (0.0015% and 0.004%) is not clinically significant.

Both concentrations of AL-6221 (0.0015% and 0.004%) are associated with ocular hyperemia. The prevalence and severity of ocular hyperemia are concentration related.

The iris/eyelash photographs read by masked independent readers reveal iris pigmentation change beginning at 1.5 months after commencement of therapy for AL-6221 0.0015% and beginning at Month 3 for AL-6221 0.004%. The prevalence increases with duration of therapy for both concentrations of AL-6221.

The iris/eyelash photographs read by masked independent readers reveal a concentration related change in eyelash color, length, density, and thickness consistent with an ocularly administered prostaglandin-type effect. The prevalence increases with duration of therapy.

8.1.6 Synopsis of Protocol C-99-18

A multicenter, double-masked, randomized. parallel group study with two phases designed to compare the efficacy of AL-6221 0.0015% BID versus placebo/vehicle BID versus a AL-6221 0.0015%/Brimonidine 0.2% BID combination. Phase 1 consists of a four-week run in period where all enrolled subjects are dosed with AL-6221 0.0015% QD. Phase 2 consists of a six-week period where all enrolled subjects are treated with either 1) AL-6221 0.0015% BID plus Brimonidine 0.2% BID, 2) AL-6221 0.0015% BID plus AL-6221 Vehicle BID, or 3) AL-6221 Vehicle BID.

Reviewer's Comments:

This study utilizes a dosing regimen, BID versus QD for AL-6221 that differs from the dosing regimen studied in the other four efficacy and safety studies submitted with this application. Also, the recommended dosing regimen for Brimonidine 0.2% is TID whereas, the drug is administered BID in this study. For these reasons, the utility of this study is questionable.

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9 Overview of Efficacy

The IOP lowering ability of AL-6221 0.0015% and AL-6221 0.004% dosed once daily in the evening is not superior to Timoptic 0.5% dosed twice daily

The IOP lowering ability of AL-6221 0.0015% and AL-6221 0.004% dosed once daily in the evening is not superior to Xalatan 0.005% dosed once daily in the evening.

AL-6221 0.0015% and AL-6221 0.004% dosed once daily in the evening lower IOP by a similar amount, approximately 6-7 mmHg and 7-8 mmHg, respectively.

In patients with mean baseline IOP of 24.2 to 26.4 mmHg, AL-6221 0.0015% and AL-6221 0.004% dosed once daily in the evening when used adjunctively with Timoptic 0.5% twice daily additionally lower IOP by approximately 4.0 mmHg and 4.5 to 5.0 mmHg, respectively.

Summary of IOP Reduction

	Change in mean IOP from Baseline (mmHg)			
Treatment	**Protocol C-97-71 Study 2**	**Protocol C-97-72 Study 3**	**Protocol C-97-79 Study 5**	**Protocol C-97-73 Study 4**
AL-6221 0.0015%	-6.0 to -7.7	-5.9 to –7.5	-7.1 to –8.3	
AL-6221 0.004%	-6.6 to –8.1	-6.6 to –8.0	-8.0 to –8.9	
Timoptic 0.5%	-4.7 to 7.1	-5.2 to –7.0	-6.3 to –7.9	
Xalatan 0.005%	-6.2 to 8.1			
AL-6221 0.0015% + Timoptic 0.5%				-5.1 to –6.7
AL-6221 0.004% + Timoptic 0.5%				-5.7 to –7.2
AL-6221 Vehicle + Timoptic 0.5%				-1.3 to –2.8

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10 Overview of Safety

Both concentrations of AL-6221 (0.0015% and 0.004%) are associated with ocular hyperemia which is concentration related.

Both concentrations of AL-6221 (0.0015% and 0.004%) are associated with a concentration related change in eyelash color, length, density, and thickness which increases with duration of therapy.

Iris pigmentation change is observed with both concentrations of AL-6221 (0.0015% and 0.004%) and is seen with greater frequency with AL-6221 0.0015%. The prevalence of iris pigmentation change increases with duration of therapy.

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Summary of Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates Greater than 1%

Adverse Event	AL-6221 0.0015%				AL-6221 0.004%					Timoptic 0.5%			AL-6221 Vehicle	Xalatan 0.005%
Protocol	C-97-71 Study 2 (N=205)	C-97-72 Study 3 (N=202)	C-97-73 Study 4 (N=142)	C-97-79 Study 5 (N=190)	C-97-02 Study 1 (N=48)	C-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=201)	C-97-73 Study 4 (N=145)	C-97-79 Study 5 (N=197)	C-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=202)	C-97-79 Study 5 (N=197)	C-97-73 Study 4 (N=145)	C-97-71 Study 2 (N=196)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
[redacted]														
Hyperemia Eye	78 (38.0)	59 (29.2)	33 (23.2)	50 (26.3)	3 (6.3)	99 (49.5)	86 (42.8)	52 (35.9)	69 (35.0)	28 (14.0)	18 (8.9)	15 (8.1)	13 (9.4)	54 (27.6)
Conjunctivitis			2 (1.4)	2 (1.1)		4 (2.0)	3 (1.5)	2 (1.4)	3 (1.5)		3 (1.5)	2 (1.1)		
Hemorrhage Subconjunctival	3 (1.5)	3 (1.5)				3 (1.5)	3 (1.5)							8 (4.1)
Keratitis	5 (2.4)	6 (3.0)	7 (4.9)			7 (3.5)	8 (4.0)	3 (2.1)		5 (2.5)	4 (2.0)		5 (3.6)	4 (2.0)
Staining Corneal					1 (2.1)									
Pruritus Eye	8 (3.9)	7 (3.5)	4 (2.8)	7 (3.7)	5 (10.4)	15 (7.5)	12 (6.0)	5 (3.4)	15 (7.6)	4 (2.0)	5 (2.5)	3 (1.6)	2 (1.4)	12 (6.1)
Blepharitis			3 (2.1)	3 (1.6)		7 (3.5)	3 (1.5)	2 (1.4)						7 (3.6)
Lid Margin Crusting							3 (1.5)							
Sticky Sensation								2 (1.4)						
Meibomitis									3 (1.5)					
Lid Disease								3 (2.1)				2 (1.1)		
Hair Disease									3 (1.5)					
Discomfort Eye	11 (5.4)	5 (2.5)	7 (4.9)	15 (7.9)	1 (2.1)	15 (7.5)	5 (2.5)	7 (4.8)	14 (7.1)	15 (7.5)	9 (4.5)	7 (3.8)	3 (2.2)	5 (2.6)
Eye Fatigue								2 (1.4)						
Pain Eye	6 (2.9)	3 (1.5)	3 (2.1)	3 (1.6)	1 (2.1)	16 (8.0)	12 (6.0)	6 (4.1)	4 (2.0)	3 (1.5)				7 (3.6)
Tearing					2 (4.2)		4 (2.0)	3 (2.1)		4 (2.0)			2 (1.1)	3 (1.5)
Foreign Body Sensation	5 (2.4)	4 (2.0)	3 (2.1)	5 (2.6)	1 (2.1)	14 (7.0)	6 (3.0)	4 (2.8)	3 (1.5)					6 (3.1)
Dry Eye	5 (2.4)	3 (1.5)		3 (1.6)	1 (2.1)	9 (4.5)	6 (3.0)	8 (5.5)	4 (2.0)	3 (1.5)	4 (2.0)			
Visual Acuity Decrease	12 (5.9)	9 (4.5)	4 (2.8)	2 (1.1)		17 (8.5)	10 (5.0)	6 (4.1)		19 (9.5)	9 (4.5)	7 (3.8)	5 (3.6)	9 (4.6)
Vision Decrease											4 (2.0)			
Vision Abnormal	3 (1.5)					4 (2.0)							2 (1.4)	
Vision Blurred	6 (3.0)		3 (2.1)	3 (1.6)		6 (3.0)	5 (2.5)	3 (2.1)		6 (3.0)	6 (3.0)	3 (1.6)	2 (1.4)	9 (4.6)
Cataract	6 (2.9)					5 (2.5)				3 (1.5)		2 (1.1)		
Cataract Nos	4 (2.0)			3 (1.6)		9 (4.5)			3 (1.5)	4 (2.0)		3 (1.6)		5 (2.6)
Aqueous Flare	3 (1.5)		5 (3.5)	2 (1.1)		3 (1.5)	3 (1.5)	2 (1.4)		3 (1.5)					
Inflammatory Cells Aqueous	4 (2.0)		7 (4.9)	3 (1.6)		4 (2.0)	3 (1.5)	6 (4.1)		4 (2.0)		2 (1.1)		
Iritis	3 (1.5)		2 (1.4)											
Photophobia					1 (2.1)	4 (2.0)		4 (2.8)		3 (1.5)				3 (1.5)
Browache					1 (2.1)									

Adverse Event	AL-6221 0.0015%				AL-6221 0.004%					Timoptic 0.5%			AL-6221 Vehicle	Xalatan 0.005%
Protocol	C-97-71 Study 2 (N=205)	C-97-72 Study 3 (N=202)	C-97-73 Study 4 (N=142)	C-97-79 Study 5 (N=190)	C-97-02 Study 1 (N=48)	C-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=201)	C-97-73 Study 4 (N=145)	C-97-79 Study 5 (N=197)	C-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=202)	C-97-79 Study 5 (N=197)	C-97-73 Study 4 (N=145)	C-97-71 Study 2 (N=196)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Iris Discolor	10 (4.9)			10 (5.3)		6 (3.0)			7 (3.6)					10 (5.1)
Eye Disease	7 (3.4)		3 (2.1)			3 (1.5)				3 (1.5)				4 (2.0)
Retinal Disease				3 (1.6)										3 (1.5)
Retinal Pigment										3 (1.5)				
Hemorrhage Retinal			2 (1.4)							5 (2.5)				
Vitreous Disease	4 (2.0)		2 (1.4)											
Vitreous Detachment						3 (1.5)								
Optic Nerve Disease									4 (2.0)					2 (1.4)
Pallor Optic Disc										3 (1.5)				
Visual Field Defect				2 (1.1)								2 (1.1)		3 (1.5)
Medical Procedure			2 (1.4)			4 (2.0)								
[redacted]														
Medical Procedure	22 (10.7)	10 (5.0)	5 (3.5)	7 (3.7)		19 (9.5)	5 (2.5)	4 (2.8)	7 (3.6)	24 (12.0)	6 (3.0)	9 (4.8)	6 (4.3)	26 (13.3)
Infection	9 (4.4)	12 (5.9)	7 (4.9)	6 (3.2)		11 (5.5)	7 (3.5)	3 (2.1)	5 (2.5)	14 (7.0)	8 (4.0)	5 (2.7)	3 (2.2)	10 (5.1)
Cold Syndrome	9 (4.4)	4 (2.0)	4 (2.8)	3 (1.6)		6 (3.0)		3 (2.1)		7 (3.5)	3 (1.5)	3 (1.6)		
Flu Syndrome	4 (2.0)			5 (2.6)		3 (1.5)		2 (1.4)	14 (7.1)	6 (3.0)		4 (2.2)	2 (1.4)	3 (1.5)
Pain	5 (2.4)	5 (2.5)		4 (2.1)		8 (4.0)			4 (2.0)	6 (3.0)	5 (2.5)	5 (2.7)	4 (2.9)	3 (1.5)
Headache	4 (2.0)	6 (3.0)	2 (1.4)	3 (1.6)		8 (4.0)		2 (1.4)	9 (4.6)	5 (2.5)	3 (1.5)			5 (2.6)
Pain Chest				2 (1.1)			3 (1.5)					2 (1.1)		
Pain Back			3 (2.1)	4 (2.1)		3 (1.5)						2 (1.1)		6 (3.1)
Pain Abdomen				3 (1.6)								2 (1.1)		
Asthenia				2 (1.1)								4 (2.2)		
Injury Accidental	6 (2.9)		5 (3.5)	3 (1.6)	1 (2.1)	8 (4.0)	6 (3.0)			5 (2.5)		5 (2.7)	3 (2.2)	4 (2.0)
Allergy		3 (1.5)	3 (2.1)	3 (1.6)				2 (1.4)						5 (2..6)
Allergic Reaction			2 (1.4)											
Carcinoma												3 (1.6)		
Hypertension	12 (5.9)	4 (2.0)	5 (3.5)	9 (4.7)	1 (2.1)	13 (6.5)		2 (1.4)	11 (5.6)	9 (4.5)	3 (1.5)	12 (6.5)	2 (1.4)	7 (3.6)
Hypotension			2 (1.4)			3 (1.5)								3 (1.5)
Bradycardia						4 (2.0)					3 (1.5)			
Coronary Artery Disease													2 (1.4)	
Cardiovascular Disease														4 (2.0)
Angina Pectoris				2 (1.1)		4 (2.0)				3 (1.5)				
Arrhythmia	5 (2.4)													
GI Disease	3 (1.5)					3 (1.5)	3 (1.5)		4 (2.0)	3 (1.5)		6 (3.2)	3 (2.2)	
Colitis									2 (1.1)					
Constipation			2 (1.4)											

Adverse Event	AL-6221 0.0015%				AL-6221 0.004%					[illegible] 0.5%			AL-6221 Vehicle	[illegible] 0.005%
Protocol	C-97-71 Study 2 (N=205)	C-97-72 Study 3 (N=202)	C-97-73 Study 4 (N=142)	C-97-79 Study 5 (N=190)	C-97-02 Study 1 (N=48)	C-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=201)	C-97-73 Study 4 (N=145)	C-97-79 Study 5 (N=197)	C-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=202)	C-97-79 Study 5 (N=197)	C-97-73 Study 4 (N=145)	C-97-71 Study 2 (N=196)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Diarrhea				2 (1.1)										3 (1.5)
Dyspepsia						3 (1.5)				3 (1.5)			2 (1.4)	3 (1.5)
Nausea														4 (2.0)
Diabetes Mellitus				2 (1.1)								2 (1.1)		5 (2.6)
Hypothyroidism												2 (1.1)		
Hypercholesterol-emia	7 (3.4)			4 (2.1)		4 (2.0)	6 (3.0)			4 (2.0)	3 (1.5)	3 (1.6)		5 (2.6)
Hyperlipidemia										3 (1.5)	3 (1.5)			
Arthritis	6 (2.9)		3 (2.1)	2 (2.1)		4 (2.0)				4 (2.0)				3 (1.5)
Arthritis Rheumatoid				2 (2.1)										
Bone Fracture			2 (1.4)				3 (1.5)							
Myalgia	5 (2.4)			2 (2.1)										
Arthrosis				3 (1.6)										
Dizziness			2 (1.4)	7 (3.7)										
Insomnia	3 (1.5)		2 (1.4)											
Anxiety				2 (1.1)		3 (1.5)							2(1.4)	
Depression						5 (2.5)		2 (1.4)		4 (2.0)		2 (1.1)		
Vertigo				2 (1.1)										
Rhinitis	7 (3.4)			4 (2.1)					3 (1.5)			3 (1.6)	3 (2.2)	
Sinusitis	4 (2.0)	3 (1.5)	3 (2.1)	2 (1.1)		10 (5.0)		3 (2.1)		5 (2.5)		3 (1.6)	2 (1.4)	5 (2.6)
Bronchitis	3 (1.5)	3 (1.5)		5 (2.6)		5 (2.5)					3 (1.5)	3 (1.6)		3 (1.5)
Cough Increase	3 (1.5)	3 (1.5)									3 (1.5)	2 (1.1)		
Pharyngitis.	3 (1.5)	4 (2.0)										5 (2.7)		
Pneumonia	3 (1.5)	2 (1.4)								3 (1.5)	3 (1.5)			
Dyspnea			2 (1.4)	3 (1.6)										
Asthma												2 (1.1)		
Dermatitis			2 (1.4)						3 (1.5)					3 (1.5)
Pruritus				2 (1.1)										
Herpes Zoster				2 (1.1)										
Otitis Media			3 (2.1)											
Infection Urinary Tract	6 (2.9)	3 (1.5)				5 (2.5)		3 (2.1)		3 (1.5)				10 (5.1)
Cystitis				3 (1.6)						3 (1.5)				
Incontinence Urinary						3 (1.5)								
Prostate Disease							3 (1.5)	2 (1.4)						
Menopause									4 (2.0)					

7 pages of revised draft labeling have been redacted from this portion of the document.

12 Conclusions

Although both concentrations of Travatan (travoprost ophthalmic solution), 0.004% and 0.0015% demonstrate efficacy in lowering IOP, Travatan 0.004% lowers IOP more than Travatan 0.0015%. The amount of IOP reduction produced by Travatan 0.004% (7-8 mmHg) as compared to Travatan 0.0015% (6-7 mmHg) is not statistically and clinically significant.

In patients with mean baseline IOP of approximately 24-26 mmHg, Travatan 0.004% dosed once daily when used adjunctively with Timoptic 0.5% dosed twice daily additionally lowers IOP by approximately 4-5 mmHg.

A significant change in iris color may signal the ability of travoprost to increase the number of melansomes (pigment granules) in melanocytes. The long term effect on melanocytes and the consequence of potential injury to melanocytes and/or disposition of pigment granules to other areas of the eye are currently unknown.

APPEARS THIS WAY
ON ORIGINAL

13 Recommendations

a. *Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-257 (TRAVATAN™ (travoprost ophthalmic solution) 0.004%) is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are intolerant of other IOP lowering medications or insufficiently responsive to another IOP lowering medication.*

b. *The applicant should submit revised labeling consistent with the recommendations in this review.*

c. *The applicant should also propose a post-marketing plan to adequately address concerns raised by the report of increased iris pigmentation and the potential for change in eyelash color, length, density, and thickness over time.*

d. *The applicant should conduct a study to evaluate potential pigmentation in the trabecular meshwork in patients undergoing a trabeculectomy after at least two years of treatment with Travatan.*

See electronic signature, page

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
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HFD-725/Biostats/Choi
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257

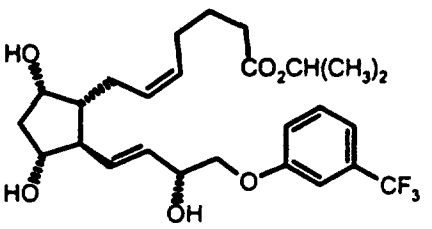
NDA 21-257
Medical Officer's Review #2

Submission Date: 07/07/00
Review Completed: 11/20/00

Proposed Trademark: Travatan 0.0015% and 0.004% ophthalmic solutions

Generic Name: Travoprost 0.0015% and 0.004% ophthalmic solutions

Chemical Name:



MW 500.56
Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

Sponsor: Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Investigator's Financial Disclosure Information: Submitted in Volume 165

Reviewer's Comments:

The original NDA submission identified eight investigators with financial interests who participated in the four covered clinical studies (C-97-71, C-97-72, C-97-73 and C-97-79) included in the NDA submission. Three of the investigators participated in two of the studies. Five were principal investigators and three were co-investigators. These investigators represent only 8 sites out of over 150 sites. If these investigators were excluded, there would be no significant impact on the result of the studies each investigator participated in.

Recommendation:

Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-257 (TRAVATAN™ (travoprost ophthalmic solution) 0.004%) is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are intolerant of other IOP lowering medications or insufficiently responsive to another IOP lowering medication.

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
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HFD-550/Chem/Fenselau
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257
120-Day Safety Update

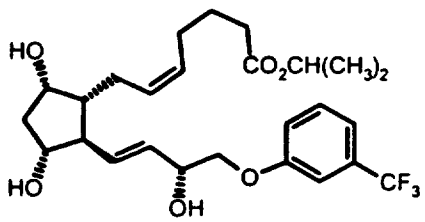
NDA 21-257
Medical Officer's Review

Submission Date: 11/06/00
Review Completed: 12/05/00

Proposed Trade name: Travatan 0.0015% and 0.004% ophthalmic solutions

Generic Name: Travoprost 0.0015% and 0.004% ophthalmic solutions

Chemical Name:



MW 500.56

Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

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CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
Contact: Scott Krueger
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Adverse Event	AL-6221 0.004%						
Study Completion Date	Pre NDA Filing					Post NDA Filing	
Protocol	C-97-82 Study 1 (N=48)	[illegible]-97-71 Study 2 (N=200)	C-97-72 Study 3 (N=201)	C-97-73 Study 4 (N=145)	C-97-79 Study 5 (N=197)	C-99-97 Study 6 (N=24)	C-98-09 Study 7 (N=30)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Vision Abnormal		4 (2.0)					
Vision Blurred		6 (3.0)	5 (2.5)	3 (2.1)			
Cataract		5 (2.5)					1 (3.3)
Cataract Nos		9 (4.5)			3 (1.5)		
Aqueous Flare		3 (1.5)	3 (1.5)	2 (1.4)			5 (16.7)
Inflammatory Cells Aqueous		4 (2.0)	3 (1.5)	6 (4.1)			2 (6.7)
Iritis							1 (3.3)
Photophobia	1 (2.1)	4 (2.0)		4 (2.8)		3 (12.5)	2 (6.7)
Browache	1 (2.1)						
Iris Discolor		6 (3.0)			7 (3.6)		
Eye Disease		3 (1.5)					
Vitreous Detachment		3 (1.5)					
Optic Nerve Disease					4 (2.0)		
Medical Procedure		4 (2.0)					
[illegible]							
Medical Procedure		19 (9.5)	5 (2.5)	4 (2.8)	7 (3.6)		1 (3.3)
Infection		11 (5.5)	7 (3.5)	3 (2.1)	5 (2.5)		
Cold Syndrome		6 (3.0)		3 (2.1)			
Flu Syndrome		3 (1.5)		2 (1.4)	14 (7.1)		
Pain		8 (4.0)			4 (2.0)		
Headache		8 (4.0)		2 (1.4)	9 (4.6)	4 (16.7)	1 (3.3)
Pain Chest			3 (1.5)				
Pain Back		3 (1.5)					
Injury Accidental	1 (2.1)	8 (4.0)	6 (3.0)				
Allergy				2 (1.4)			
Hypertension	1 (2.1)	13 (6.5)		2 (1.4)	11 (5.6)	1 (4.2)	
Hypotension		3 (1.5)					
Bradycardia		4 (2.0)					
Angina Pectoris		4 (2.0)					
GI Disease		3 (1.5)	3 (1.5)		4 (2.0)		
Colitis					2 (1.1)		
Dyspepsia		3 (1.5)					
Cholecystitis							1 (3.3)
Hypercholesterol-emia		4 (2.0)	6 (3.0)				
Liver Function Abnormal						1 (4.2)	
Arthritis		4 (2.0)					
Bone Fracture			3 (1.5)				
Somnolence						1 (4.2)	
Anxiety		3 (1.5)					
Depression		5 (2.5)		2 (1.4)			
Rhinitis					3 (1.5)		
Sinusitis		10 (5.0)		3 (2.1)			
Bronchitis		5 (2.5)					
Dermatitis					3 (1.5)	-	1 (3.3)
Skin Discoloration							1 (3.3)
Infection Nail							1 (3.3)
Infection Urinary Tract		5 (2.5)		3 (2.1)		1 (4.2)	
Incontinence Urinary		3 (1.5)					
Prostate Disease			3 (1.5)	2 (1.4)			
Menopause					4 (2.0)		

[redacted]

Reviewer's Comments:

Such a high incidence of LFT abnormalities has not been previously reported. Liver function was evaluated in two of the studies submitted with the original NDA (Protocols C-97-71 and C-97-92), in which 808 subjects were exposed to Travoprost 0.0015% or 0.004%. The five subjects with LFT elevations represent only a small fraction of those who have been exposed to Travoprost.

Conclusive evidence that would explain the abnormal LFT findings has not been identified. Hence, the three subjects whose liver function tests have not yet normalized should be followed until the values return to baseline. The protocol for any future study should include evaluation of hepatic function.

Summary of Reviewer's Recommendations:

1) *The three subjects whose liver function tests have not yet normalized should be followed until the values return to baseline.*
2) *The protocol for any future study should include evaluation of hepatic function.*

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
HFD-550/Div Files
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HFD-725/Biostats/Choi
HFD-550/Chem/Fenselau
HFD-550/Pharm Tox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257

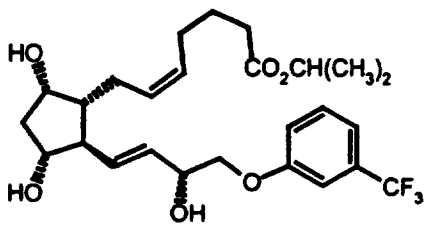
NDA 21-257
Medical Officer's Review #4

Submission Date: 01/04/01
Review Completed: 01/22/01

Proposed Trademark: Travatan 0.0015% and 0.004% ophthalmic solutions

Generic Name: Travoprost 0.0015% and 0.004% ophthalmic solutions

Chemical Name:



MW 500.56
Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

Sponsor:

Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Submitted:

Submitted are sponsor's responses to the 14 issues detailed in the Approvable letter dated 12/22/2000.

Reviewer's Comments/Problem List:

1) Sponsor's responses to clinical issues 12, 13, and 14 are acceptable.

2) The safety data contained in the final clinical study reports for Studies C-99-97 (Renal PK study) and C-98-09 (Open-Label Study conducted in Mexico) submitted with this submission is comparable to that reported in the original NDA and 120-day safety update.

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
HFD-550/Div Files
HFD-550/MO/Lim
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HFD-725/Biostats/Choi
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257

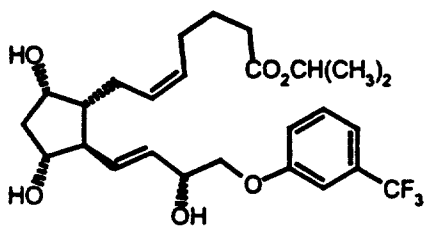
NDA 21-257
Medical Officer's Review #3

Submission Date: 01/04/01
Review Completed: 01/22/01

Proposed Trademark: Travatan 0.0015% and 0.004% ophthalmic solutions

Generic Name: Travoprost 0.0015% and 0.004% ophthalmic solutions

Chemical Name:



MW 500.56
Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

Sponsor:

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P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Submitted:

Submitted is a proposal to revise the carton, foil overwrap, and container labels.

Reviewer's Comments/Problem List:

1) The "Inactives" section of the carton label should be modified to read as follows:

> ***Inactives:*** *poloyxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water.*

2) The established and proprietary names for the drug as they appear on the carton label should be modified so as to be in compliance with the regulatory requirements set forth in 21 CFR §201.10 (g)(2).

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
HFD-550/Div Files
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HFD-880/Biopharm/Adebowale
HFD-725/Biostats/Choi
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257

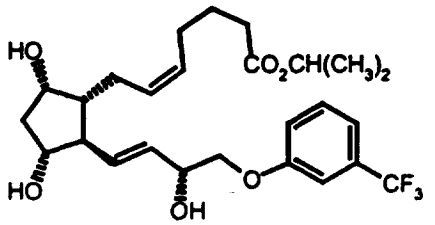
NDA 21-257
Medical Officer's Review #6

Submission Date: 01/18/01
Review Completed: 01/26/01

Proposed Trademark: Travatan 0.004% ophthalmic solution

Generic Name: Travoprost 0.004% ophthalmic solution

Chemical Name:



MW 500.56
Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

Sponsor:

Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Submitted:

Submitted is the revised the carton, foil overwrap, and container labeling for both trade and professional sample products.

Reviewer's Comments:

The carton, foil overwrap, and container labeling for both trade and professional sample products have been revised as recommended by the agency and is now acceptable.

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
HFD-550/Div Files
HFD-550/MO/Lim
HFD-550/Dep Director/Chambers
HFD-550/Acting Div Director/Bull
HFD-880/Biopharm/Adebowale
HFD-725/Biostats/Choi
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257

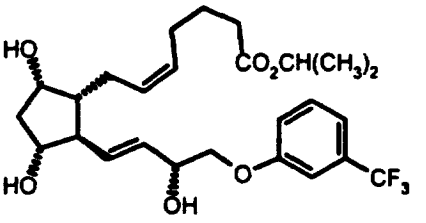
NDA 21-257
Medical Officer's Review #5

Submission Date: 01/04/01
Review Completed: 02/14/01

Proposed Trademark: Travatan 0.004% ophthalmic solution

Generic Name: Travoprost 0.004% ophthalmic solution

Chemical Name:



MW 500.56
Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

Sponsor:

Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Submitted: Submitted is sponsor's proposal to revise the package insert.

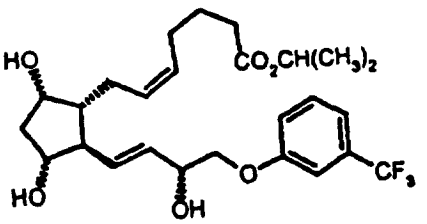
Reviewer's Comments:

Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.

TRAVATAN™ (travoprost ophthalmic solution) 0.004%
Sterile

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.56. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN™ Ophthalmic Solution 0.004% is supplied as a sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN™ 0.004% contains 40 µg travoprost. Benzalkonium chloride 0.015% is added as a preservative. Inactive ingredients are polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption: Travoprost is absorbed through the cornea. In humans, peak plasma concentrations of travoprost free acid (25 pg/mL or less) were reached within 30 minutes following topical ocular administration and was rapidly eliminated.

Metabolism: Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Excretion: Elimination of travoprost free acid from human plasma is rapid. Plasma levels are below the limit of quantitation (< 10 pg/mL) within one hour following ocular instillation.

INDICATIONS AND USAGE

TRAVATAN™ Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CLINICAL STUDIES

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25-27 mmHg were treated with TRAVATAN Ophthalmic Solution 0.004% dosed once-daily in the evening

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24-26 mmHg on TIMOPTIC 0.5% BID who were treated with TRAVATAN ™ 0.004% dosed QD adjunctively to TIMOPTIC® 0.5% BID demonstrated 6-7 mmHg reductions in intraocular pressure.

CONTRAINDICATIONS

Known hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product. TRAVATAN™ may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

WARNINGS

TRAVATAN™ has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

TRAVATAN™ may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

TRAVATAN™ may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. [redacted]

PRECAUTIONS

General

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). Iris pigmentation changes may be more noticeable in patients with mixed colored irises, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation ensues.

TRAVATAN™ should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN™ should be used with caution in these patients.

TRAVATAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

TRAVATAN™ has not been studied in patients with renal or hepatic impairment and should be used with caution in such patients.

TRAVATAN™ should not be administered while wearing contact lenses.

Patients should be advised that TRAVATAN ™ contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN™.

Since prostaglandins are biologically active and may be absorbed through the skin, women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area with soap and water immediately.

Information for Patients

Patients should be advised concerning all the information contained in the Warnings and Precautions sections.

Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Travoprost was not mutagenic in Ames test, mouse micronucleus tests and rat chromosome aberration assay. However, a slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day [250 times the maximum recommended human ocular dose of 0.04 µg/kg/day on a µg/kg basis for (MRHOD)]. At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implanation losses were increased. These effects were not observed at 3 µg/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects

Pregnancy Category: C

Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 µg/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 µg/kg/day (75 times the MRHOD), and in mice at subcutaneous doses up to 1.0 µg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 µg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses ≥ 0.12 ug/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

No adequate and well-controlled studies have been performed in pregnant women. TRAVATAN ™ may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN™ is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common ocular adverse event observed in controlled clinical studies with TRAVATAN 0.004% was ocular hyperemia which was reported in 35 to 50% of patients.

Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse events reported at an incidence of 1 to 4% included abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN™ should not exceed once-daily, since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration, and the maximum effect is reached after 12 hours.

TRAVATAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

TRAVATAN™ (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER ® package system inside a sealed foil pouch. TRAVATAN ™ is supplied as a 2.5 mL solution in a 3.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0065-0266-25, 2.5 mL fill

Storage

Store between 2°[illegible]25°C (36°[illegible]77°F). Discard the container within 6 weeks of removing it from the sealed pouch.

R_x Only

U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; and 6,011,062.

ALCON LOGO
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Recommended Regulatory Action:

The package insert is recommended for approval provided the changes noted above are made by the applicant.

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 21-257
HFD-550/Div Files
HFD-550/MO/Lim
HFD-550/Dep Director/Chambers
HFD-550/Acting Div Director/Bull
HFD-880/Biopharm/Adebowale
HFD-725/Biostats/Choi
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

Medical Officer's Review of NDA 21-257

NDA 21-257

Submission Dates: 02/15/01, 02/28/01, 03/01/01

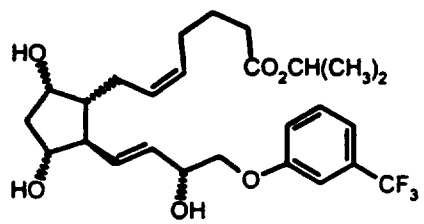
Medical Officer's Review #7

Review Completed: 03/07/01

Proposed Trademark: Travatan 0.004% ophthalmic solution

Generic Name: Travoprost 0.004% ophthalmic solution

Chemical Name:



MW 500.56

Travoprost $C_{26}H_{35}F_3O_6$.

[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-mrthylethyl ester

Sponsor:

Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

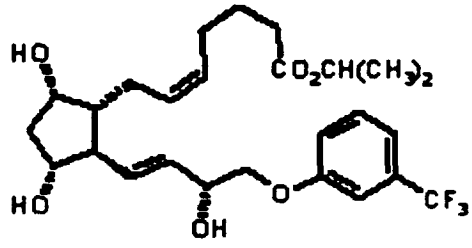
Submitted: Submitted are three proposals to revise the package insert.

TRAVATAN™ (travoprost ophthalmic solution) 0.004%

Sterile

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5S)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.56. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN™ Ophthalmic Solution 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN™ 0.004% contains 40 *u*g travoprost. Benzalkonium chloride 0.015% is added as a preservative. Inactive Ingredients are: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption: Travoprost is absorbed through the cornea. In humans, peak plasma concentrations of travoprost free acid (25 pg/mL or less) were reached within 30 minutes following topical ocular administration and was rapidly eliminated.

Metabolism: Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Excretion: Elimination of travoprost free acid from human plasma is rapid. Plasma levels are below the limit of quantitation (<10 pg/mL) within one hour following ocular instillation.

Clinical Studies

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25 – 27 mmHg who were treated with TRAVATAN Ophthalmic Solution 0.004% dosed once-daily in the evening demonstrated 7 – 8 mmHg reductions in intraocular pressure. In subgroup analyses of these studies, mean IOP reduction in black patients was up to 1.8 mmHg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24 – 26 mmHg on TIMOPTIC* 0.5% BID who were treated with TRAVATAN™ 0.004% dosed QD adjunctively to TIMOPTIC® 0.5% BID demonstrated 6 – 7 mmHg reductions in intraocular pressure.

INDICATIONS AND USAGE

TRAVATAN™ Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Known hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product. TRAVATAN™ may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

WARNINGS

TRAVATAN™ has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

TRAVATAN™ may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has been reported in association with the use of TRAVATAN™.

TRAVATAN™ may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). Iris pigmentation changes may be more noticeable in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information about increased brown pigmentation is

available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation ensues.

TRAVATAN™ should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN™ should be used with caution in these patients.

TRAVATAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

TRAVATAN™ has not been studied in patients with renal or hepatic impairment and should be used with caution in such patients.

TRAVATAN™ should not be administered while wearing contact lenses.

Patients should be advised that TRAVATAN™ contains benzalkonium chloride which may be adsorbed by contact lenses. Contact lenses should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN™.

Since prostaglandins are biologically active and may be absorbed through the skin, women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area with soap and water immediately.

Information for Patients

Patients should be advised concerning all the information contained in the Warnings and Precautions sections.

Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 *u*g/kg/day [250 times the maximum recommended human ocular dose of 0.04 *u*g/kg/day on a *u*g/kg basis (MRHOD)]. At 10 *u*g/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 *u*g/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects

Pregnancy Category: C

Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 *u*g/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 *u*g/kg/day (75 times the MRHOD), and in mice at subcutaneous doses up to 1.0 *u*g/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 *u*g/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 *u*g/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of $\geq$ 0.12 *u*g/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

No adequate and well-controlled studies have been performed in pregnant women. TRAVATAN™ may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN™ is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common ocular adverse event observed in controlled clinical studies with TRAVATAN™ 0.004% was ocular hyperemia which was reported in 35 to 50% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse events reported at an incidence of 1 to 4% included, abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at a rate of 1 to 5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN™ should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration, and the maximum effect is reached after 12 hours.

TRAVATAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

TRAVATAN™ (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER® package system inside a sealed foil pouch.

TRAVATAN™ is supplied as a 2.5 mL solution in a 3.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0065-0266-25, 2.5 mL fill

Storage

Store between 2° – 25°C (36° – 77°F). Discard the container within 6 weeks of removing it from the sealed pouch.

R_x Only

U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; and 6,011,062.

*TIMOPTIC is a registered trademark of Merck & Co., Inc.

ALCON LOGO
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Recommended Regulatory Action:

The above package insert is recommended for approval.

Lucious Lim, M.D., M.P.H.
Medical Officer