CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-275 SUBMISSION DATE: 09/18/00

PRODUCT: Lumigan™
(Brimatoprost Ophthalmic Solution, 0.03%)

SPONSOR: Allergan
Irvine, CA

REVIEWER: Veneeta Tandon, Ph.D.

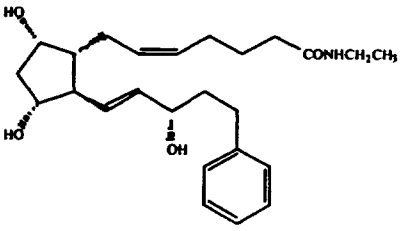
I. BACKGROUND

Drug Classification: 1P

Dosage Form: Ophthalmic solution, 0.03%

Indication: For the lowering of intraocular pressure (IOP) in patients with open angle glaucoma or hypertension.

Pharmacologic Class: A prostamide, a synthetic analogue of prostaglandin F2α. Mechanism of action of lowering IOP by increasing outflow of aqueous humor both through trabecular meshwork and uveoscleral routes.



Clinical Endpoints: Lowering of IOP.

Dosage and administration: One drop in the affected eye(s) once daily in the evening.

Foreign marketing history: Brimatoprost (AGN 192024) ophthalmic solution has not been marketed in any country yet.

Formulation: The formulation of LUMIGAN™ Ophthalmic Solution 0.03% is shown in the following table.

Ingredient	Concentration (%w/v)
Brimatoprost (AGN 192024)	0.03
Benzalkonium Chloride	0.005
Sodium Chloride	[redacted]
Sodium Phosphate	
Citric Acid	
1N Hydrochloric Acid	
1N Sodium Hydroxide	
Purified Water	

II. OVERVIEW OF SYSTEMIC EXPOSURE OF TOPICAL BRIMATOPROST OPHTHALMIC SOLUTION

Brimatoprost is systemically absorbed under clinical use condition (one drop once daily in the evening). Brimatoprost appears in the blood stream in about 6-7 minutes, and the concentrations are below the limit of quantitation by 3 hours in all subjects. No accumulation was observed upon multiple dosing for 14 days. The half-life to brimatoprost upon IV dosing was about 45 minutes, hence any accumulation is unlikely.

III. RECOMMENDATION

The clinical pharmacokinetics section of the NDA is acceptable. The labeling changes on page 11 of the review should be conveyed to the sponsor.

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TABLE OF CONTENTS

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IV. OVERALL SUMMARY OF CLINICAL PHARMACOKINETICS STUDIES:

Is the analytical validation for the detection of brimatoprost and its metabolite acceptable?

Yes, the analytical validation is acceptable.

Is brimatoprost metabolized in humans?

Brimatoprost is the main circulating species in the human blood. Brimatoprost undergoes gluronidation, hydroxylation, N-deethylation and deamidation to form a wide variety of metabolites. The glucoronide was the most abundant metabolite, but the structure could not be identified. C-1 acid metabolite (AGN 191522) was the minor metabolite. These metabolites were investigated following intravenous administration of ^{3}H-AGN 192024 to human subjects. The metabolic scheme proposed by the sponsor is attached in the Appendix on pages 14-15.
The in vitro metabolism studies have been reviewed by the Pharmacologist, Dr. Zhou Chen.

Is brimatoprost systemically absorbed upon topical application of 0.03% brimatoprost ophthalmic solution under clinical use conditions?

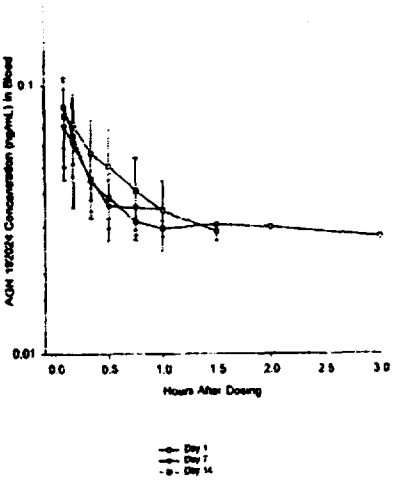
Brimatoprost is systemically absorbed upon topical application. There was a large inter-individual variability seen in systemic exposure. The peak concentrations reached rapidly (6-8 minutes) and fell below the limit of quantitation in 1-1.5 hours post dosing. No accumulation was observed after once daily dosing for 14 days. The sponsor has evaluated the systemic exposure of brimatoprost from a clinical pharmacokinetic study as well as from therapeutic drug monitoring during clinical trials. Once daily (proposed clinical use regimen) as well as twice daily dosing regimens have been studied in both pharmacokinetic studies and clinical efficacy trials. The results from these studies will be discussed in this section.

The systemic absorption has been evaluated under clinical use conditions (one drop once daily in the evening) in study PK-98-119/192024-006.

Population: 14 healthy adults (13M & 1F)
Dose and duration: one drop of 0.03% brimatoprost ophthalmic solution once daily in the evening for 14 days
Blood samples: Days 1, 7 and 14 at 0, 5, 10, 20 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose.

The mean pharmacokinetic parameters and the mean plasma concentration time profile of brimpatoprost for Day 1, 7 and 14 is shown in the following table and figure.

Collection Day		C_{max} (ng/mL)	t_{max} (hour)	AUC_{0-t} (ng hr/mL)
1	Mean	0.0864	0.105	0.0318
	SD	0.02050	0.0364	0.02455
	n	15	15	15
7	Mean	0.0721	0.131	0.0259
	SD	0.02504	0.0711	0.01186
	n	14	14	14
14	Mean	0.0822	0.107	0.0444
	SD	0.02525	0.0394	0.02067
	n	14	14	14



The individual subject pharmacokinetic parameters for Day 1, 7 and 14 are attached in the Appendix on page 16.

Conclusions:

- Brimatoprost rapidly appears in the blood stream (6-7 minutes) and concentrations fell below the LOQ by 1.5 hours, except in one subject, where concentrations went below the LOQ at 3 hours post dose.
- The C_{max}'s and AUC_{0-t}'s were similar between Day 1 and 7 and that between Days 1 and 14. This indicates that there was no accumulation upon multiple dosing.
- The C1-acid metabolite AGN 191522 was not detected in human blood.

Therapeutic Drug Monitoring:

The sponsor has evaluated the blood concentrations of brimatoprost and its metabolite from two Phase 3 clinical trials (Study 192024-008 and 009). The two regimens evaluated in these 3 month trials were:

1. Brimatoprost administered once daily in the evening (N=36 and 52 patients, respectively for the two clinical trials)

2. Brimatoprost administered twice daily in the morning and the evening (N=37 and 27 patients, respectively for the two clinical trials)

Blood samples were taken 5 minutes post dose at Day 0 (first day of dosing) and Month 3 (last day of dosing). The tmax from the pharmacokinetic studies was approximately 6-8 minutes. The mean concentrations obtained are shown in the following table. In this table "N" stands for the number of samples with brimatoprost concentrations.

Study 192024-008

	AGN 192024 QD		AGN 192024 BID	
	Day 0	Month 3	Day 0	Month 3
N	35	26	31	28
Mean (ng/mL)	0.078	0.073	0.064	0.100
SD (ng/mL)	0.051	0.041	0.045	0.054

Study 192024-009

	AGN 192024 QD		AGN 192024 BID	
	Day 0	Month 3	Day 0	Month 3
N	51	50	51	44
Mean	0.064	0.062	0.074	0.068
SD	0.039	0.035	0.056	0.043

Conclusions:

- There was no systemic accumulation of brimatoprost after once daily dosing from either clinical trial, but there was a statistically significant accumulation after twice daily dosing ($p = 0.0037$) based on results from Study 008, but not from Study 009. Hence, the clinical relevance of the observed accumulation cannot be determined.
- The sponsor also evaluated the effect of age, weight, body surface area and gender on the concentrations of brimatoprost. Brimatoprost concentrations were found to be dependent on only age at the first day of dosing (Day 0, $p= 0.0457$) and did not affect brimatoprost concentrations at Month 3 based on results of Study 008, however from Study 009, brimatoprost concentrations were dependent on age at Month 3 ($p=0.0031$). The different results from the two studies can only suggest that age does affect the brimatoprost concentrations, but the clinical relevance cannot be clearly defined.

The sponsor has also evaluated the systemic absorption of brimatoprost and it C1-acid metabolite under non-clinical dosing conditions (bilateral twice daily dosing, in the morning and evening) in a clinical pharmacokinetic study (Study PK-99-040/192024-007).

Population: 15 healthy adults (12M & 3F), 13 completed study

Dose and duration: one drop of 0.03% brimatoprost ophthalmic solution twice daily in the morning and evening for 14 days

Blood samples: On Days 1, 7 and 14 following the evening dose at 0, 5, 10, 15, 20 30, 45 minutes and 1, 1.5, 2, 3, 4 and 12 hours post evening dose. On Days 2, 8 and 15 following the morning dose at 5, 10, 15, 20 30, 45 minutes and 1, 1.5, 2, 3, 4 and 12 hours post morning dose.

The pharmacokinetic parameters on the various collection days are shown in the following table.

Parameter		Collection Day					
		1	2	7	8	14	15
C_{max}	Mean	0.0575	0.0924	0.109	0.136	0.112	0.136
(ng/mL)	SD	0.02358	0.03735	0.0215	0.0326	0.0250	0.0638
	n	14	14	14	14	13	13
t_{max}	Mean	0.089	0.083	0.107	0.089	0.089	0.083
(hours)	SD	0.0224	0	0.0394	0.0224	0.0233	0
	n	14	14	14	14	13	13
AUC_{TLAC}	Mean	0.0146	0.0176	0.0413	0.0571	0.056	0.0505
(ng*hr/mL)	SD	0.00639	0.00992	0.01915	0.02868	0.02763	0.0314
	n	10	13	14	14	13	13
AUC[a]	Mean	0.0262	0.0369	0.0905	0.130	0.104	0.100
(ng*hr/mL)	SD	0.00887	0.02178	0.07036	0.1002	0.0610	0.0726
	n	9	9	14	12	13	13
Daily Exposure[b]	Mean	NA	0.0580	NA	0.225	NA	0.204
	SD	NA	0.01618	NA	0.1518	NA	0.1226
	n	NA	7	NA	12	NA	13

a AUC_∞ was similar to AUC 12 on Day 1
b The sum of AUC12 values following morning and evening doses within a 24 hr period

Conclusions:

- Brimatoprost rapidly appears in the blood stream (5-6.5 minutes) and concentrations fell below the LOQ by 2-3 hours.
- The C_{max}'s and AUC_{0-t}'s were statistically different on Days 7, 8, 14 and 15 as compared to that on Days 1 and 2 (see p-values in Appendix on page 18).
- The mean C_{max} following the morning dose on Days 2, 8 and 15 were 20 to 60% higher than those following the evening dose.
- The average daily exposure on multiple dosing on Days 7 through 8 and Days 14 through 15 were 4 times higher than daily exposure on Days 1 through 2.
- This shows that there is some degree of accumulation upon multiple-dosing. The mean t1/2 of brimatoprost after twice daily dosing ranged from 0.230 to 1.35 hours following the evening dose and from 0.350 to 1.24 hours following the morning dose (see Appendix page 17). The t1/2 of brimatoprost after intravenous administration was 0.771±0.32 hours (about 45 minutes) from another study (Study 192024-005), hence most of the drug would be eliminated in 4-7 hours and significant accumulation would be unlikely.

- The C1-acid metabolite AGN 191522 was not detected in human blood after twice daily ophthalmic dosing.

Pharmacokinetics of brimatoprost in the young and elderly subjects:

The pharmacokinetics of 0.03% brimatoprost after topical ocular administration was evaluated in the young (<45 years) and elderly (≥ 65 years) healthy subjects after twice daily dosing for 7 days (Study 192024-005). The elderly subjects had 73% and 124% higher Cmax and AUC, respectively, compared to younger subjects. Brimatoprost concentrations were also found to be dependent on age from the therapeutic drug monitoring of the clinical trials, but the clinical relevance of the difference in brimatoprost blood concentrations cannot be explained.

Population:	45 healthy adults (21M & 24F), out of which there were 22 young (11M & 11F) subjects and 23 (10M &13F) elderly subjects.
Dose and duration:	one drop of 0.03% brimatoprost ophthalmic solution twice daily in the morning and evening for 7 days
Blood samples:	On Days 1 and 7 following the evening dose at 0, 5, 10, 20 30, 45 minutes and 1, 1.5, 2, 3, 4 and 12 hours post evening dose. On Days 2 and 8 following the morning dose at 5, 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4 and 12 hours post morning dose.

The pharmacokinetic parameters in the young and elderly subjects on Day 1 and 7 are shown in the following table.

Group	Statistic	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)
		← Day =1 →			← Day =7 →		
Young	N	19	22	22	21	22	22
	Mean	0.1649	0.0451	0.0129	0.1294	0.0540	0.0099
	CV%	94.2	54.1	146.2	48.0	53.9	71.1
Elderly	N	23	23	23	21	21	21
	Mean	0.1536	0.0781	0.0289	0.1055	0.0844	0.0310
	CV%	89.2	45.5	136.0	34.7	45.6	168.1

The p-values comparing the young vs. elderly and Day 1 vs. Day 7 are shown in the following tables.

p-value for two-sample t-test (Elderly vs Young)			
	C_{max}	AUC_{0-t}	AUC_{0-t} (without outliers)[a]
Day 1	0.001	0.090	0.009
Day 7	0.006	0.099	0.015

a Subject 1027 and 1036 on Day 1 and subject 1002 on Day 7

p-value for paired t-test (Day 1 vs Day 7 data)			
	C_{max}	AUC_{0-t}	AUC_{0-t} (without outliers)[a]
Young	0.238	0.465	0.886
Elderly	0.303	0.535	0.435

a Subject 1027 and 1036 on Day 1 and subject 1002 on Day 7

The individual subject C_{max} and AUC_{0-t} are shown graphically in the Appendix on page 21.

Conclusions:

- The mean C_{max} and AUC_{0-t} values for the elderly group were 73% and 124% higher than that for the young group for Day 1 and were 56% and 213% higher on Day 7, respectively. This difference was statistically significant for C_{max}, but not for AUC_{0-t}. However, there were 3 subjects that had unusually high AUCs. After removing these three subjects the AUC was significantly different between the two groups. These differences cannot be explained by the difference in body weight. The mean body weight of the elderly group was 14% higher than the young group. The difference seen in the brimatoprost concentrations in the young and elderly population is not clinically relevant. (Please refer to Clinical Review by Dr. W. Boyd)
- There was no significant difference in the C_{max} and AUC_{0-t} at Day 1 vs. Day 7, indicating no significant accumulation upon multiple dosing. This is contradictory to Study 192024-007 (twice daily dosing), in which significant accumulation was observed. However, twice daily dosing is not the to-be-marketed dosing regimen for 0.03% brimatoprost ophthalmic solution.
- Blood samples of brimatoprost were below the limit of quantification by 1.5 hours in both the young and elderly subjects.
- C-1 acid metabolite was not detected in the blood.

What are the other disposition characteristics (distribution and elimination) of brimatoprost?

The major route of elimination of brimatoprost is by renal elimination. About 67% of the administered dose was excreted in the urine and about 25% is excreted via the feces after an intravenous administration. Brimatoprost is moderately distributed into the tissues with a Vss of 0.670L/kg. The elimination t1/2 of brimatoprost was 0.771 hours (46 minutes).

The sponsor has conducted a mass balance radiolabeled study with intravenous ^{3}H-AGN 192024 to evaluate the disposition characteristics of brimatoprost.

Population: 6 healthy male adults

Dose and duration:	0.01% of ^{3}H-AGN 192024 administered as a single intravenous bolus over approximately 10 seconds. The radiological dose was 3.28± 0.12 µCi/kg in a volume of 0.03 mL/Kg
Blood samples:	At predose, 2, 5, 10, 15, 30 and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 9, 12, 18, 24, 30, 36, 48, 72, 96, 120, 144, and 168 hours post dose. Blood was drawn from contralateral arm (i.e. contralateral to dosing arm) for the 24 hours after dosing, after which it could be drawn from either arm.
Urine samples:	At the following intervals, -10-0 hour, 0-2, 2-4, 4-6, 6-9, 9-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours post dose.
Fecal samples:	At the following intervals, -10-0 hour, 0-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours post dose.

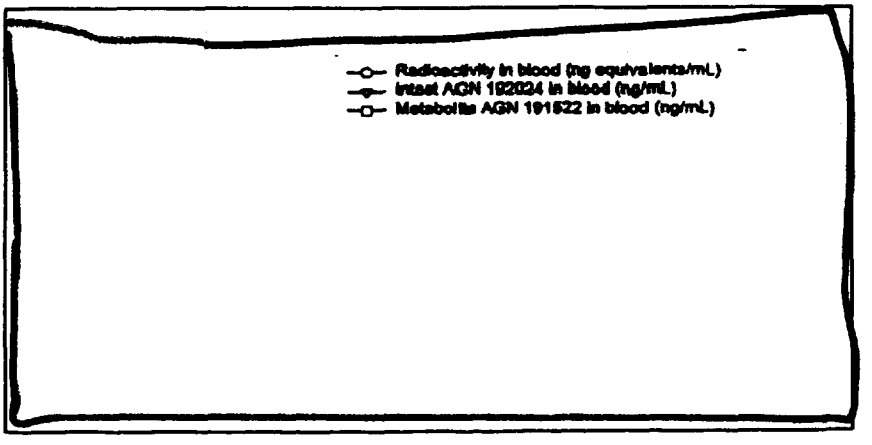
The mean (±SD) values for the major pharmacokinetic parameters for brimatoprost and the radioactivity is shown in the following table:

Pharmacokinetic Parameter	Radioactivity		192024
	Blood	Plasma	Blood
AUC_{0-TLOC} (ng•hour/mL)[a]			
$AUC_{0-\infty}$ (ng•hour/mL)			
K ($hour^{-1}$)			
$t_{1/2}$ (hour)			
Cl (L/hour)			
Cl (L/hour/kg)			
V_{z} (L)			
V_{z} (L/kg)			

a Blood and plasma radioactivity, ng equivalents•hour/mL.

The individual subject values for blood/plasma radioactivity and brimatoprost blood concentrations are attached in the Appendix on page 19. The percent of radioactive dose excreted in the urine, feces and toilet tissue for each subject is attached in the Appendix on page 20.

The concentration-time profiles are shown in the following figure:



Conclusions:

- There is a rapid distribution phase followed by a gradual elimination of radioactivity.
- Maximum concentrations of radioactivity in both blood and plasma were reached at the first collection time point, at 2 minutes post-dose.
- Blood concentrations of intact brimatoprost declined steadily with time and were below the limit of quantitation by 3-6 hours post-dose with a mean t1/2 of 0.771 hours.
- The Vss was 0.670 L/kg.
- The metabolite AGN 191522 was detected in 4 out of the 6 subjects and only between 0.083-1.5 hours post-dose. The concentration of the metabolite was lower than that of the parent drug.
- The amount of radioactivity in blood is higher than that of the parent compound detected in blood, suggesting the presence of circulating metabolites in the blood. As mentioned earlier there were many metabolites of brimatoprost, many of which were not structurally identified.
- Renal excretion was the prevalent route of elimination of the radioactivity, with approximately 67% of the administered dose excreted in the urine and 25% of the dose recovered in the feces. The mean overall recovery of radioactivity in the excreta was 92%.

V. LABELING

The following labeling changes in "Pharmacokinetics" sub-section under "Clinical Pharmacology" section should be conveyed to the sponsor.

Pharmacokinetics

Absorption:

[redacted] After one drop of [redacted] ophthalmic solution was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing, and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. [redacted] There was no significant systemic drug accumulation over time with once daily dosing.

Distribution

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma. [redacted]

Metabolism

Bimatoprost is not extensively metabolized in the human eye and it is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes [redacted] N-deethylation and [redacted] to form a diverse variety of metabolites. [redacted]

Elimination

Following an intravenous dose of radiolabeled bimatoprost (3.12 μg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL [redacted] and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

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CC: NDA 21-275
HFD-550/Div File
HFD-550/CSO/Puglisi
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)

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9 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.