CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-214

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-214 SUBMISSION DATE: 2/15/00, 4/26/00 5/5/00, 5/12/00, 6/12/00, 6/16/00

PRODUCT: Rescula®, 0.15% (Unoprostone isopropyl ophthalmic solution)

SPONSOR: Ciba Vison Georgia REVIEWER: Veneeta Tandon, Ph.D.

REVIEW OF A NDA

I. BACKGROUND

Drug Classification: 1P

Dosage Form: Ophthalmic solution for topical application (Unoprostone isopropyl 0.15%)

Indication: For the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension

Pharmacologic Class: Docasanoid: these are cyclic derivatives of arachidonic acid and include $PGF_{2\alpha}$ and other eicosanoids. They are chemically differentiated from eicosanoids by having a carbon chain length of 22 (two more than eicosanoids). It is believed to reduce elevated IOP, by increasing the outflow of aqueous humor without stimulating prostaglandin receptors or any other known intraocular pressure reducing receptors.

Dosage and Administration: One drop to the affected eye(s) twice daily.

Foreign Marketing History: Rescula®, 0.12% marketed in Japan since 1994 and in 28 other countries since 1997 onwards.

Formulation:

Ingredient	mg/mL
Unoprostone Isopropyl	
Polysorbate 80, NF	
Benzalkonium chloride, NF	0.15
Edetate disodium, USP	
Mannitol, USP	
Sodium hydroxide, NF Hydrochloric acid,	
Water for Injection, USP	

II. RECOMMENDATION

The Human Pharmacokinetics section of this application is not acceptable. Comment to the sponsor on page 6 should be forwarded. The analytical validation report in terms of the long-term stability of the plasma samples had not been completed at the time of this submission. The study report itself was submitted to the agency on 4/26/00. The validity of the study results can only be assessed upon the completion of the evaluation of the long-term stability of the plasma samples for the duration prior to the analysis for drug and metabolite content. Hence, the labeling recommendations have been deferred. No human pharmacokinetics information can be provided in the label at this time. The label should clearly state that the information provided is solely based on animal data.

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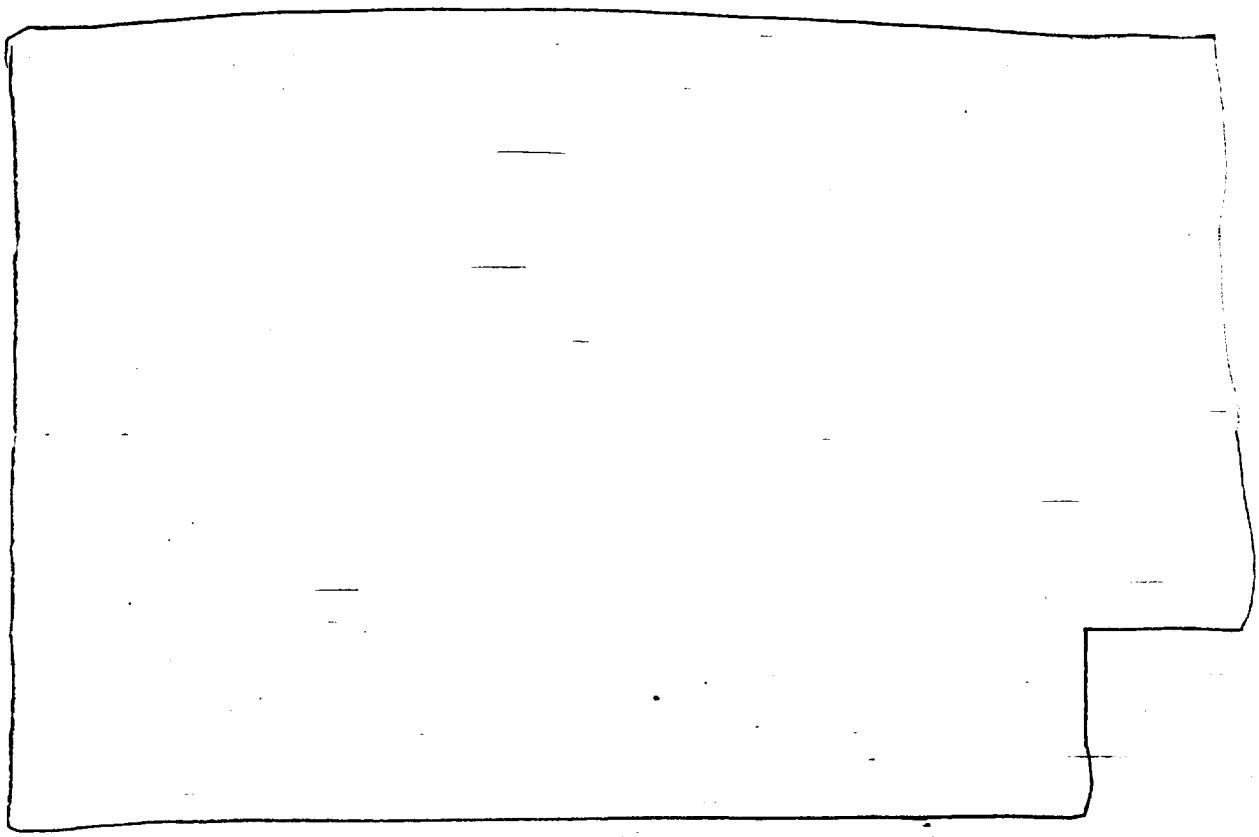
III. ANALYTICAL VALIDATION



1 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

III. . PHARMACOKINETIC STUDIES

A pharmacokinetic study of unoprostone isopropyl 0.15% ophthalmic solution in healthy volunteers following ocular administration b.i.d. for 14 days (Protocol Number C99-UIOS-018)

This study was conducted to determine the pharmacokinetic parameters of unoprostone isopropyl 0.15% ophthalmic solution after first topical administration in each eye on Day 1 and again after last topical dose in each eye on Day 14 following b.i.d. dosing in each eye for 14 days.

This was a single center, open label trial in 18 healthy subjects (9F & 9M). Mean age of the patients was 38 years. Regarding race, 17 subjects were Caucasians and 1 subject was Asian. The demographics are attached in the Appendix on page 8. Subjects received one drop of the solution (lot number 90858) into the conjunctival sac of each eye b.i.d. Blood samples were collected at 15 minutes predose, and at 5, 15, 30 and 45 minutes postdose and at 1, 2, 4, 8 and 12 hours post dose. The systemic absorption of unoprostone and its metabolite M1 was evaluated.

Plasma levels of unoprostone isopropyl

All plasma unoprostone isopropyl concentrations at every time point were below the analytical limit of quantitation (<0.5 ng/mL) on Day 1 as well as Day 14.

Plasma levels of metabolite M1

The M1 concentrations dropped below the limit of quantitation (0.25 ng/mL) in most subjects by 30 minutes post dose and in all subjects by one hour post dose on both Day 1 and Day 14. Two subjects showed plasma levels of M1 at 45 minutes postdose on Day 1 and one subject at 45 minutes post dose on Day 14. The individual M1 plasma concentrations on Day 1 and Day 14 are attached in the Appendix on page 9.

The mean plasma M1 pharmacokinetic parameters on Day 1 and Day 14 are shown in the following table. The individual subject plasma pharmacokinetic parameters are attached in the Appendix on page 10.

Day	Variables	N	Mean	CV (%)	Minimum	Maximum
1	C_{max} (ng/mL)	18	0.576	70.02	0.000	1.49
	T_{max} (h)	16	0.202	38.7	0.0833	0.271
	AUC_{0-t} (ng.h/mL)	18	0.140	129.7	0.000	0.615
14	C_{max} (ng/mL)	18	0.526	80.38	0.000	1.300
	T_{max} (h)	14	0.208	40.5	0.083	0.325
	AUC_{0-t} (ng.h/mL)	18	0.146	107.1	0.000	0.447
	R (accumulation ratio)	16	1.979	163.0	0.000	13.167

Observations

- Very high inter-individual variability was observed as reflected by the %CVs.
- For most subjects the accumulation ratio (R) ranged from approximately [redacted] Two subjects had a large accumulation ratio of [redacted] (Subject 1) and [redacted] (Subjects 8). Subject 1 did not show any plasma levels of M1 after 30 minutes and Subject 8 had the last detectable plasma level of M1 at 45 minutes post dose.
- None of the subjects had plasma levels of M1 at one hour post dose on Days 1 and 14.
- The sponsor has reported the $t_{1/2}$ from Subject 11 as approximately 14 minutes. However, the calculation of AUC_{0-inf} and $t_{1/2}$ in this case may not be very reliable (see Appendix page 9)
- The highest plasma level of M1 seen in any subject was 1.5 ng/mL (Subject 11).

IV. OVERALL CONCLUSIONS

- The analytical validation for M1 and UI was not complete (long term validation not performed yet) and therefore unacceptable. The conclusions from the bioavailability study cannot be used for labeling purposes. The validity of the study would be confirmed once the long-term stability results are submitted and acceptable to the Agency and the following bullets would be acceptable thereafter.
  - From Study C99-UIOS-018 it was observed that unoprostone isopropyl levels were not detected in any of the plasma levels.
  - The M1 concentrations dropped below the limit of quantitation (0.25 ng/mL) in most subjects by 30 minutes post dose and in all subjects by one hour post dose on both Day 1 and Day 14.
  - The AUC_{0-t} (%CV) of M1 on Day 1 was 0.1402 ng.h/mL (129.7) and was 0.1461 (107.1) ng.h/mL on Day 14.
  - Significant accumulation was not observed in most subjects, except two. However, in these two subjects too, the plasma M1 levels were undetectable at one hour post dose.
  - In vivo and in vitro metabolism studies have been carried out in animals. Unoprostone isopropyl undergoes ester hydrolysis to M1 mainly found in plasma. M4 was mainly found in the urine, but could not be quantitated in humans. Although human liver microsomes were not used in the in vitro metabolism study, the involvement of CYP 450s is unlikely as the major pathway of metabolism is ester hydrolysis (see chemical structures)

IV. LABEL

The label for the Clinical Pharmacology section should not contain any human pharmacokinetics information until the long term stability studies with plasma samples for the detection of unoprostone isopropyl and metabolite M1 have been evaluated and its impact on the interpretation of the results from the human study is determined.

V. COMMENTS TO THE SPONSOR

- The long-term stability of the plasma samples for the determination of unoprostone isopropyl and M1 should be submitted to the Agency for the validation of the analytical procedure used in Study C99-UIOS-018. Results from this study cannot be used for labeling purposes, until the validation of the assay has been submitted, reviewed and found acceptable.

/S/ 6/29/00

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D /S/ 6/30/00

CC: NDA 21-214
HFD-550/Div File
HFD-550/CSO/Rodriguez
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPENDIX

NDA 21-214

Table 14.1.2. Demographic Information for All Subjects

Subject Number	Initials	Randomized Treatment	Treatment Received	Gender	Age (Years)	Height (cm)	Weight (kg)	Frame	Smoking Habits	Race	Completed Study According to Protocol?	Included in Safety Analysis ?	Included in PK Analysis ?
1		A	A	Male	45	170	70.8	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
2		A	A	Female	19	163	55.4	Small	Nonsmoker	Caucasian	Yes	Yes	Yes
3		A	A	Female	44	165	62.6	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
4		A	A	Male	41	183	99.4	Large	Nonsmoker	Caucasian	Yes	Yes	Yes
5		A	A	Female	46	163	77.2	Large	Nonsmoker	Caucasian	Yes	Yes	Yes
6		A	A	Male	37	180	71.7	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
7		A	A	Female	35	165	55.8	Small	Nonsmoker	Caucasian	Yes	Yes	Yes
8		A	A	Male	32	183	143.5	Large	Nonsmoker	Caucasian	Yes	Yes	Yes
9		A	A	Female	38	163	74.5	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
10		A	A	Male	59	175	74	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
11		A	A	Female	60	165	72.6	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
12		A	A	Male	28	178	108.5	Large	Nonsmoker	Caucasian	Yes	Yes	Yes
13		A	A	Female	29	158	79.9	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
14		A	A	Male	20	191	94	Large	Nonsmoker	Caucasian	Yes	Yes	Yes
15		A	A	Female	39	175	51.3	Small	Nonsmoker	Caucasian	Yes	Yes	Yes
16		A	A	Male	31	183	74	Medium	Nonsmoker	Asian	Yes	Yes	Yes
17		A	A	Female	56	160	64.9	Medium	Nonsmoker	Caucasian	Yes	Yes	Yes
18		A	A	Male	22	175	99.9	Large	Nonsmoker	Caucasian	Yes	Yes	Yes

Treatment A = Unoprostone Isopropyl 0.15% Ophthalmic Solution

Table 14.2.3. Plasma M1 Concentrations (ng/mL) Following
Instillation of One Drop Unoprostone Isopropyl 0.15% Ophthalmic Solution Into Each Eye (Day 1)

Subject Number	Sample Times (hr) 0	0.08	0.25	0.5	0.75	1	2	4	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
Mean	0.000	0.389	0.512	0.092	0.032	0.000	0.000	0.000	0.000	0.000
S.D.	0.000	0.452	0.387	0.178	0.094	0.000	0.000	0.000	0.000	0.000
C.V.(%)	.	116.125	75.451	193.311	291.990	.	.	.	.	.
S.E.M.	0.000	0.107	0.091	0.042	0.022	0.000	0.000	0.000	0.000	0.000
N	18.000	18.000	18.000	18.000	18.000	18.000	18.000	18.000	18.000	18.000
Minimum	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maximum	0.000	1.490	1.380	0.463	0.311	0.000	0.000	0.000	0.000	0.000

Samples below the quantifiable limit of 0.250 are reported as 0.000
. = Value missing or not reportable

Table 14.2.4. Plasma M1 Concentrations (ng/mL) Following
Instillation of One Drop Unoprostone Isopropyl 0.15% Ophthalmic Solution Into Each Eye Twice Daily for 14 Days (Day 14)

Subject Number	Sample Times (hr) 311.5	312.08	312.25	312.5	312.75	313	314	316	320	324
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
Mean	0.000	0.362	0.471	0.133	0.017	0.000	0.000	0.000	0.000	0.000
S.D.	0.000	0.399	0.383	0.204	0.070	0.000	0.000	0.000	0.000	0.000
C.V.(%)	.	110.131	81.354	153.518	424.264	.	.	.	.	.
S.E.M.	0.000	0.094	0.090	0.048	0.017	0.000	0.000	0.000	0.000	0.000
N	18.000	18.000	18.000	18.000	18.000	18.000	18.000	18.000	18.000	18.000
Minimum	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maximum	0.000	1.300	1.230	0.588	0.299	0.000	0.000	0.000	0.000	0.000

Samples below the quantifiable limit of 0.250 are reported as 0.000
. = Value missing or not reportable

Table 14.2.5. Plasma M1 Pharmacokinetic Parameters Following Instillation of One Drop Unoprostone Isopropyl 0.15% Ophthalmic Solution Into Each Eye (Day 1)

	Parameters					
Subject Number	Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T1/2 hr	Kel 1/hr
1	0.568	0.251	0.04731	.	.	.
2	0.796	0.110	0.1459	.	.	.
3	0.563	0.249	0.04293	.	.	.
4	0.000	.	0.00	.	.	.
5	0.412	0.0836	0.01722	.	.	.
6	0.000	.	0.00	.	.	.
7	0.339	0.250	0.06929	.	.	.
8	0.316	0.250	0.02642	.	.	.
9	0.333	0.256	0.06803	.	.	.
10	1.260	0.250	0.5254	.	.	.
11	1.490	0.0833	0.6159	0.7196	0.231	3.00
12	0.340	0.249	0.02832	.	.	.
13	0.425	0.256	0.08610	.	.	.
14	0.346	0.249	0.02811	.	.	.
15	1.010	0.0844	0.1630	.	.	.
16	0.943	0.249	0.3078	.	.	.
17	0.826	0.0900	0.2928	.	.	.
18	0.409	0.272	0.03861	.	.	.
Mean	0.576	0.202	0.1402	0.7196	0.231	3.00
S.D.	0.404	0.0782	0.1818	.	.	.
C.V.(%)	70.026	38.7	129.7	.	.	.
S.E.M.	0.095	0.0196	0.04285	.	.	.
N	18.000	16.0	18.00	1.000	1.00	1.00
Minimum	0.000	0.0833	0.00	0.7196	0.231	3.00
Maximum	1.490	0.272	0.6159	0.7196	0.231	3.00

. = Value missing or not reportable

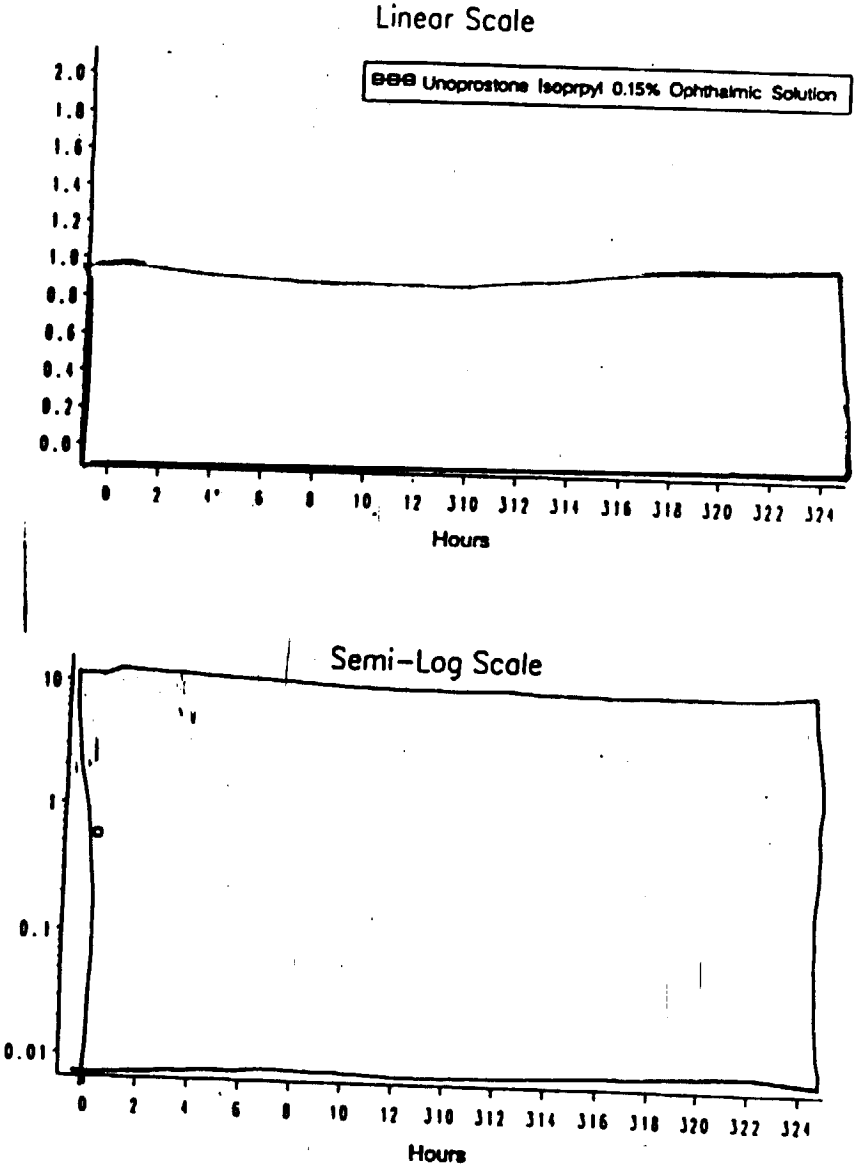
Table 14.2.6. Plasma M1 Pharmacokinetic Parameters Following Instillation of One Drop Unoprostone Isopropyl 0.15% Ophthalmic Solution Into Each Eye (Day 14)

	Parameters						
Subject Number	Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	Cavg ng*hr/mL	T1/2 hr	Kel 1/hr	R
1	0.745	0.250	0.2465	0.02054	.	.	5.21
2	0.558	0.0831	0.1120	0.00933	.	.	0.768
3	0.629	0.249	0.05205	0.00433	.	.	1.21
4	0.000	.	0.00	0.00	.	.	.
5	0.295	0.326	0.03580	0.00298	.	.	2.08
6	0.000	.	0.00	0.00	.	.	.
7	0.285	0.265	0.06174	0.00514	.	.	0.891
8	0.696	0.258	0.3479	0.02899	.	.	13.2
9	0.373	0.0831	0.07559	0.00629	.	.	1.11
10	1.230	0.248	0.4476	0.03730	.	.	0.852
11	1.230	0.248	0.4261	0.03551	.	.	0.692
12	0.000	.	0.00	0.00	.	.	0.00
13	0.443	0.247	0.03641	0.00303	.	.	0.423
14	0.300	0.248	0.05875	0.00489	.	.	2.09
15	1.300	0.0831	0.3580	0.02983	.	.	1.96
16	0.771	0.247	0.2537	0.02114	.	.	0.824
17	0.627	0.0856	0.1181	0.00984	.	.	0.403
18	0.000	.	0.00	0.00	.	.	0.00
Mean	0.527	0.209	0.1461	0.01218	.	.	1.98
S.D.	0.423	0.0844	0.1565	0.01305	.	.	3.23
C.V.(%)	80.388	40.5	107.1	107.1	.	.	163
S.E.M.	0.100	0.0226	0.03690	0.00307	.	.	0.808
N	18.000	14.0	18.00	18.00	0.00	0.00	16.0
Minimum	0.000	0.0831	0.00	0.00	.	.	0.00
Maximum	1.300	0.326	0.4476	0.03730	.	.	13.2

. = Value missing or not reportable

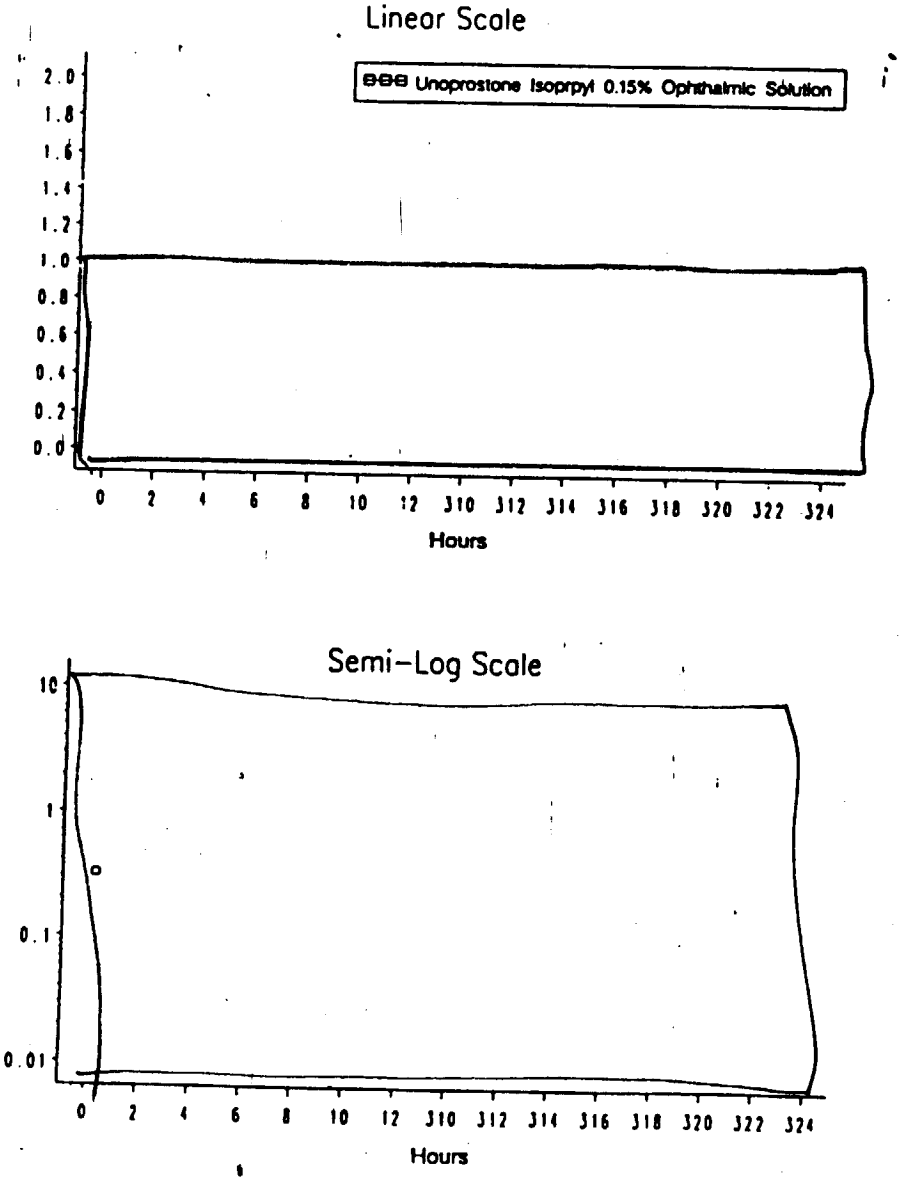
Plasma M1 Concentrations Versus Time Following Multiple Dosing Twice Daily for 14 Days

Subject 1



Plasma M1 Concentrations Versus Time Following Multiple Dosing Twice Daily for 14 Days

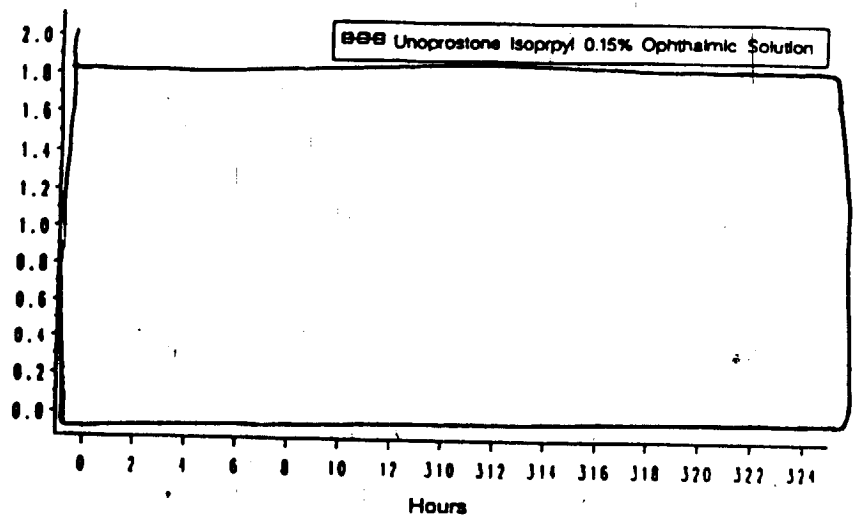
Subject 8



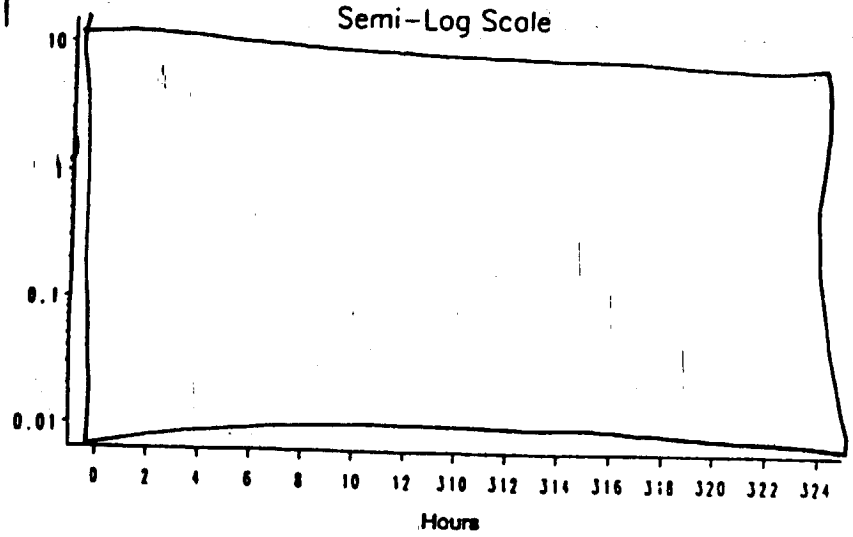
Plasma M1 Concentrations Versus Time Following Multiple Dosing Twice Daily for 14 Days

Subject 10

Lineor Scale



Semi-Log Scale

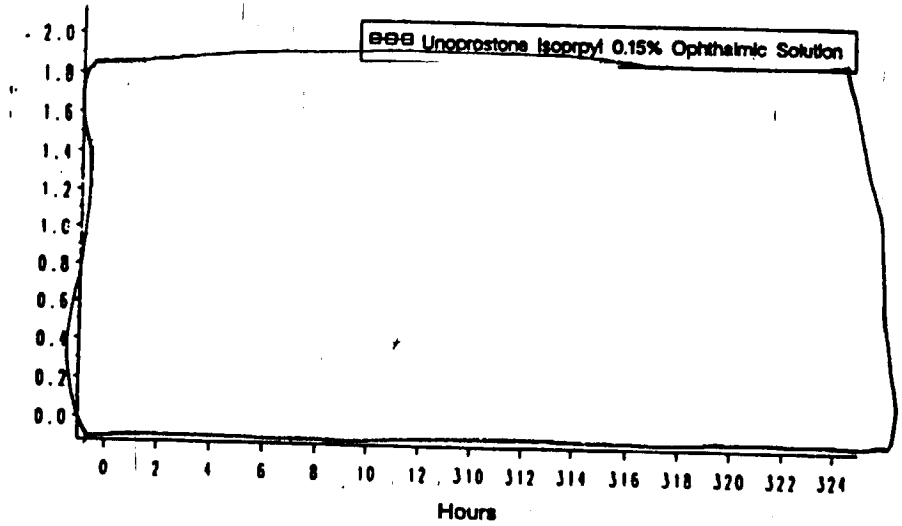


Plasma M1 Concentration (ng/mL)

Plasma M1 Concentrations Versus Time Following Multiple Dosing Twice Daily for 14 Days

Subject 11

Lineor Scale



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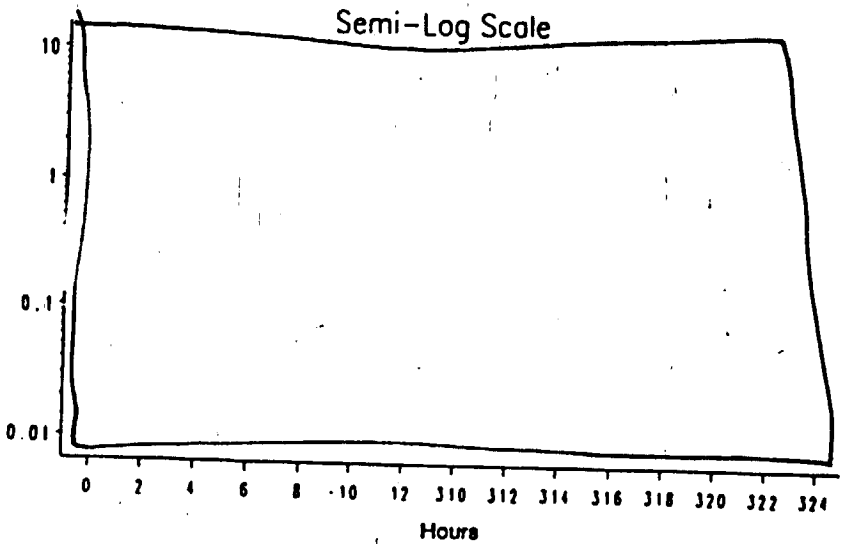

Plasma M1 Concentration (ng/mL)