CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **21-066**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Ketotifen Fumarate
Ophthalmic Soln. 0.025%
NDA 21-066 ORIG.
Reviewer: E. D. Bashaw, Pharm.D.
WO

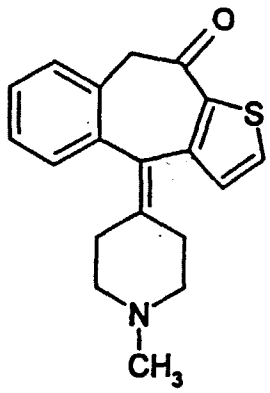
Ciba Vision/Novartis Co.
Duluth, GA 30097

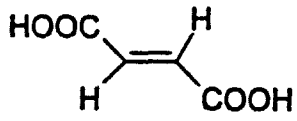
Submission Date:
Jan. 4, 1999

Review of an New Molecular Entity

I. Background

Ketotifen fumarate is a H-1 selective receptor antagonist and mast cell stabilizer. It has been used clinically in Europe, Canada, and Japan for a number of years in the treatment of asthma as both an immediate and sustained release tablet.





Chemically, ketotifen fumarate is the fumarate salt of 4-(1-Methyl-4-piperidylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10(9*H*)-one. In this submission the formulation is a 0.025% solution (0.25mg/ml) for ophthalmic instillation. The intended dose is 1 drop in the affected eye every 8-12 hours. This corresponds to a dose of 0.0125mg per eye, assuming 20 drops/ml (USP XXIII), or a maximal daily dose of 0.075mg/day.

II. Recommendation

In this submission the sponsor has not included the results of any in vivo biopharmaceutic studies using either the to-be-marketed dosage form or ophthalmic administration. They have included literature references of in vivo biostudies using other formulations (oral and injectable). From this information it is apparent that with microgram daily dosing of this compound, that even assuming 100% absorption, if one uses the smallest estimate of volume of distribution (8.8L/kg) the resulting plasma levels would be undetectable. For this reason no in vivo bioavailability studies were required. At the request of the medical staff a phase IV bioavailability study will be conducted by the sponsor to assess systemic exposure after 14 days of use. From a biopharmaceutic standpoint, the application is acceptable.

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III. Application Overview

As noted previously, there are no in vivo pharmacokinetic trials in this submission using either the to-be-marketed dosage form or route of administration. Approval of this application is based upon the results of in vivo pharmacokinetic studies conducted with both an IV and various oral dosage forms of ketotifen (none of which are approved for use in the United States). Ketotifen has been reported to have a volume of distribution, following intravenous administration, of approximately 9L/kg. Given the clinical dose of 0.075mg/day this would work out to a theoretical peak concentration (assuming 100% instantaneous bioavailability) of 0.075mg/day / (9L/kg * 70kg) = .000119 mg/L or 0.119 ng/ml or 119pg/ml. This is near the limit of detection for an assay published by Julien-Larose, et al[1] which is capable of quantifying both parent (50pg/ml) and metabolites (300pg/ml). While seeming feasible, this ignores the fact that the dose is divided throughout the day and it ignores loss of drug issues (i.e. tearing, overflow out of the conjunctiva, etc.). Given these very low doses and a clearance of 1.7L/hr/kg, it is highly unlikely that any drug or metabolites will be detected in the plasma.

[1] "Quantification of Ketotifen and its Metabolites in Human Plasma by Gas Chromatography-Mass Spectrometry" Fourth International Symposium on Quantitative Mass Spectrometry in Life Sciences, Ghent, Belgium, 1982.

The remainder of this review will summarize some of the more relevant articles submitted in this NDA and the proposed Phase IV pk study with ophthalmologic dosing.

IV. Review of Published Literature

As part of this application the applicant has submitted copies of five journal articles, 12 internal reports, and 1 conference proceeding concerning ketotifen. As noted previously, none of this material is directly relevant to the approval of an eyedrop formulation of ketotifen.

Of the five published articles, one deals with developing an in vivo-in vitro correlation with an extended release tablet, two deal with pediatric dosing issues, one is a study of first pass effects, and the last study deals with drug disposition following oral dosing. None of these studies are relevant here.

Unfortunately the internal study reports are, for the most part, also unenlightening. Most of them date to pre-1982 and use assay techiques that have been noted to cross-react with metabolites. They use small numbers of subjects and are not very well documented, some being only summaries of material previously submitted to the oral tablet NDA. The closest relevant material is from a report by Nuesch, et al. on the pharmacokinetics of ketotifen following IV, oral, and inhalation doses. This report is summarized below:

(A). [redacted]

This study was a randomized, single-blind, four-way crossover study in 8 healthy subjects (4M/4F). Each subject received each of the following treatments in a random order:

1mg IV
1mg orally
2mg orally
1mg by inhalation

Plasma samples were collected for 48hrs post dosing and analyzed for parent drug only. The results of this trial are summarized in the table below and in Supplemental Tables 1-3 and Figures 1-4 in Appendix I.

	1mg Oral	2mg Oral	1mg Inhalation	1mg IV
AUC0-48 (ng*hr/ml)	12.7+/-3.4	21.8+/-4.1	5.9+/-4.4	19.89+/-4.5
Cmax (ng/ml)	0.56+/-0.12	0.98+/-0.1	0.29+/-0.2	–
Tmax (hr.)	3.7+/-1.3	4.3+/-2.0	3.5+/-2.2	–

In addition to this data the study provided mean estimates of both V and Vβ of 518 and 1177 liters, respectively. Indicating that ketotifen is highly distributed in man. While useful this study report suffers from being too brief in nature to be very useful. That

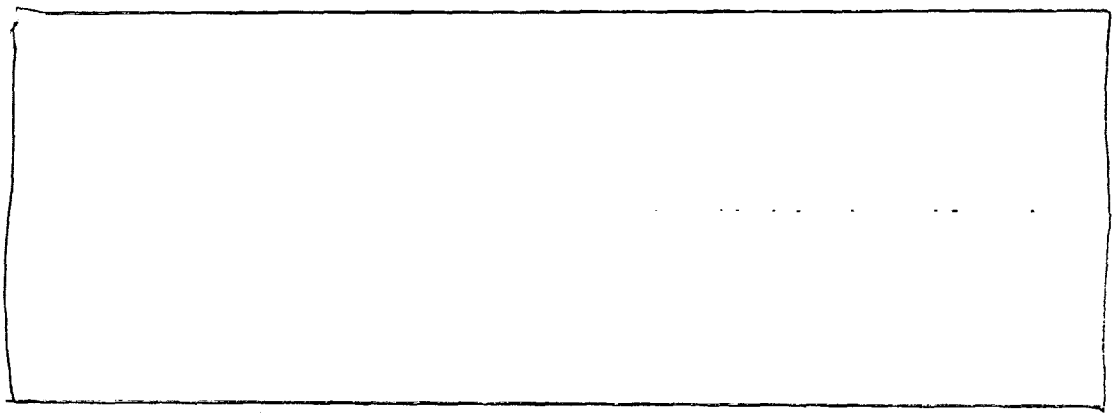
coupled with the small number of subjects (8) makes definitive interpretation difficult. This study is, however, the best study submitted in this package as it does provided a rather detailed pharmacokinetic analysis, when compared with the rest of the submitted material. The study does confirm the large volume of distribution that was cited as a reason earlier (when coupled with the dose) as to why in vivo pharmacokinetic studies would not be needed. By comparison, the dose used here (intravenously) was ~13x that proposed for ophthalmic use. Suggesting again that ophthalmic dosing is not going to result in meaningful in vivo plasma levels.

V. Phase IV Study

This study was requested by the medical staff to confirm the lack of detectable in vivo plasma levels following ophthalmologic dosing. The study will be an open label, single center study with 8 healthy subjects. On day one, each subject will be dosed with marketed ketotifen ophthalmic solution (0.025%) either 2 or 3 times daily (depending upon the approved labeling). Blood samples for ketotifen will also be collected during day 1. Following this, dosing will continue for a total of 14 days at which time plasma levels will again be collected and analyzed for ketotifen. Standard pharmacokinetic techniques will be employed to determine the pharmacokinetics of ophthalmic ketotifen along with the degree of accumulation (day 1 to 14) will be assesed.

VI. Labeling

Attached in the Appendix is the sponsors proposed package insert. At the present time the proposed package insert does not contain any information regarding in vivo pharmacokinetics. The following information should be included in the clinical pharmacology section:



VII. Comments

1.) The proposed package insert should be revised as indicated in the previous section to present some information on the pharmacokinetics of ketotifen itself.

2.) The applicant should submit their protocol for the Phase IV pk study to the Agency for comment prior to intitiation.

/S/ 5/31/99

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

Secondary Review, Arzu Selen, Ph.D., Dep. Dir. DPE-III /S/ 6/2/99

CC: NDA 21-066 (ORIG),
HFD-550/DIV File
HFD-550/CSO/Rodriquez
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

Appendix
NDA 21-066

Table I:

Subj. No.	Sex	Age (years)	Weight (kg)	Height (cm)
2	m	35	58	168
3	m	28	56	170
4	f	26	54	168
5	m	30	68	176
6	f	33	51	167
7	f	27	56	172
8	f	30	68	174
11	m	29	62	175
Mean ± SD		30 ± 3	59 ± 6	171 ± 3
± SEM		± 1	± 2	± 1
Median		29	57	171
Range		26-35	51-68	167-176

Table VI: Pharmacokinetic parameters after administration of [redacted]

Subj. No.	tmax (h)			Cp(tmax) (ng/ml)			AUC(0-48h) (ng/ml·h)			
	1 mg p.o.	2 mg p.o.	1 mg inhal.	1 mg p.o.	2 mg p.o.	1 mg inhal.	1 mg p.o.	2 mg p.o.	1 mg i.v.	1 mg inhal.
2	4.0	4.0	4.0	0.63	1.01	0.46	15.71	24.15	19.92	12.22
3	2.0	4.0	6.0	0.39	0.83	0.24	7.53	15.19	12.94	3.82
4	4.0	4.0	-	0.56	1.07	~0	10.49	22.85	19.18	0.33
5	2.0	4.0	(0.08-8)	0.39	0.85	0.19	8.00	19.05	16.91	5.36
6	4.0	2.0	4.0	0.54	1.06	0.16	11.51	17.48	18.95	1.14
7	4.0	2.0	0.25	0.59	0.94	0.50	14.77	22.85	19.08	6.25
8	4.0	8.0	1.5	0.69	0.97	0.57	15.85	26.56	27.80[1)]	12.12
11	6.0	6.0	5.0	0.69	1.12	0.23	18.05	26.03	24.33	5.61
Mean	3.7	4.3	3.5[2)]	0.56	0.98	0.29	12.74	21.77	19.89	5.86
± SD	± 1.3	± 2.0	± 2.2	± 0.12	± 0.10	± 0.20	± 3.91	± 4.11	± 4.50	± 4.43
± SEM	± 0.5	± 0.7	± 0.9	± 0.04	± 0.04	± 0.07	± 1.38	± 1.45	± 1.59	± 1.56

Remarks: 1) Calculated without Cp(0.08h) = 18.64
2) Calculated without Subject No. 5

Table II

Table VI: (continued) Pharmacokinetic parameters after administration of [redacted]

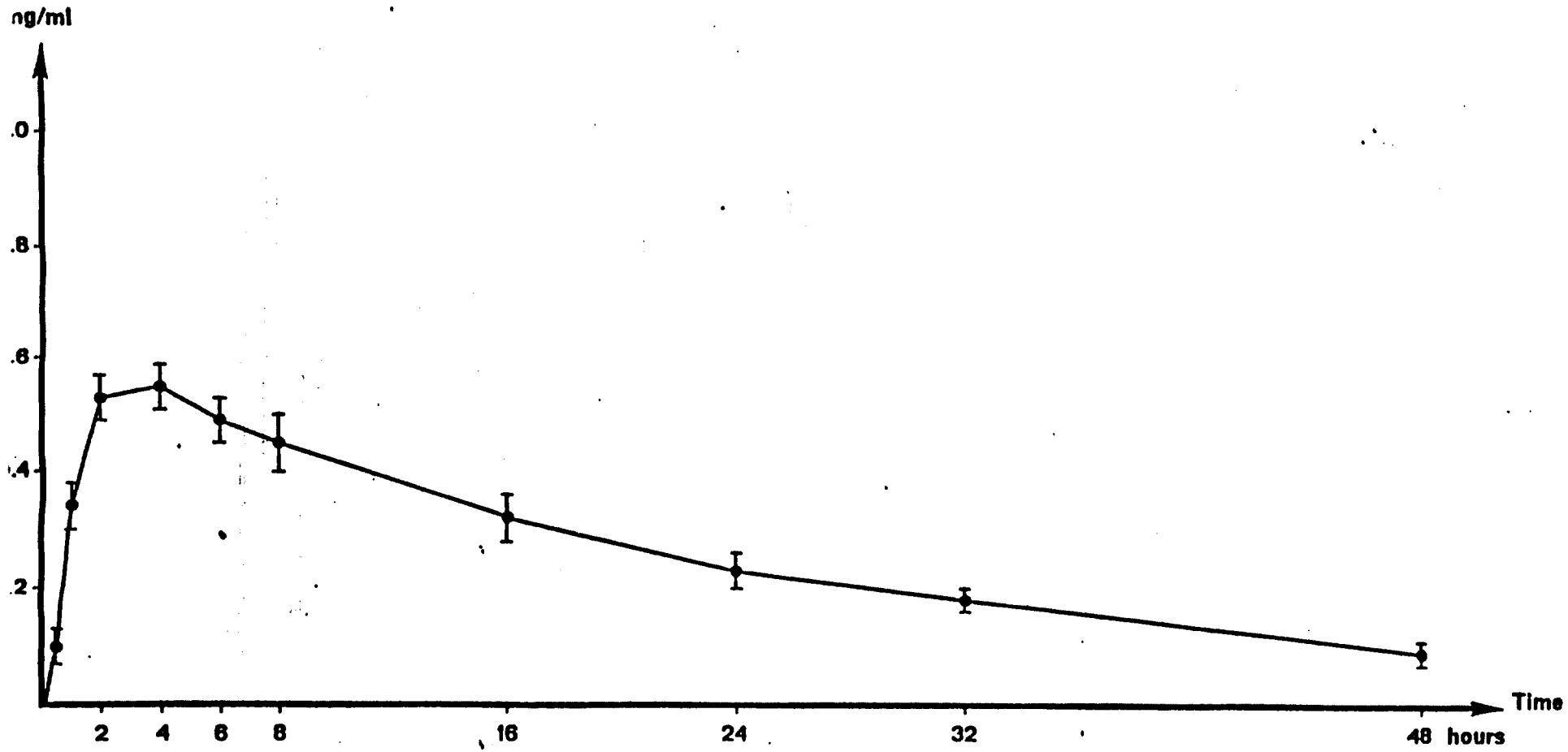
Parameters		Subject No. 2.	3	4	5	6	7	8	11	Mean ±	SD ±	SEM
α'	(h^{-1})	13.60f	—	—	—	—	—	12.91f	—	13.25 ±	0.49 ±	0.45
A'	(ng/ml)	1.998f	—	—	—	—	—	45.78f	—	23.89 ±	30.96 ±	21.89
α	(h^{-1})	0.87	1.04	0.52	2.44f	0.31f	5.11	0.41f	3.19	1.73 ±	1.71 ±	0.61
t_α	(h)	0.80	0.67	1.34	0.28	2.27	0.14	1.71	0.22	0.93 ±	0.78 ±	0.27
β	(h^{-1})	0.0351	0.0652	0.0378	0.0517	0.0344	0.0331	0.0222	0.0409	0.0401 ±	0.0131 ±	0.0046
t_β	(h)	19.7	10.6	18.3	13.4	20.1	20.9	31.2	16.9	18.9 ±	6.1 ±	2.2
k	(h^{-1})	0.045	0.108	0.097	0.208	0.114	0.089	0.071	0.085	0.102 ±	0,048 ±	0.017
k_{21}	(h^{-1})	0.683	0.625	0.203	0.606	0.092	1.902	0.127	1.536	0.722 ±	0.665 ±	0.235
k_{12}	(h^{-1})	0.177	0.368	0.257	1.677	0.134	3.156	0.229	1.608	0.951 ±	1.097 ±	0.388
V	(litres)	915	762	489	267f	397f	477	419f	415	518 ±	213 ±	75
V_β	(litres)	1158	1263	1250	1076	1321	1284	1208	861	1177 ±	149 ±	53
$AUC(\infty)^{iv}$	(ng/ml·h)	24.60	12.15	21.17	17.98	22.00	23.53	37.29	28.41	23.39 ±	7.39 ±	2.61
Cl_T	(ml/min)	677	1372	787	927	757	708	447	587	783 ±	277 ±	98
Δt_1	(h)	0.39	0.54	0.51	0.10f	0.05f	0.22	0.36f	0.51	0.33 ±	0.19 ±	0.07
Δt_2	(h)	0.53	0.66	0.79	0.30f	0.39f	0.42	0.04f	1.82	0.62 ±	0.53 ±	0.19
k_a^{po}	(h^{-1})	1.446	0,704	0.409	0.277	0.338	0.861	0.371	0.588	0.624 ±	0.388 ±	0.137
$t_{k^{po}}$	(h)	0.48	0.98	1.69	2.50	2.05	0.81	1.87	1.18	1.45 ±	0.69 ±	0.24
F^{po}	—	0.692	0.614	0.623	0.511	0.497	0.690	0.510	0.606	0.593 ±	0.079 ±	0.028
k_a^I	(h^{-1})	2.696	0.565	—	0.629	—	1.744	1.243	0.951	1.305 ±	0.808 ±	0.330
$t_{k_a^I}$	(h)	0.26	1.23	—	1.10	—	0.40	0.56	0.73	0.71 ±	0.39 ±	0.16
F^I	—	0.566	0.368	—	0.260	—	0.310	0.472	0.242	0.370 ±	0.127 ±	0.052

Remark: f: fixed parameter

14-0154

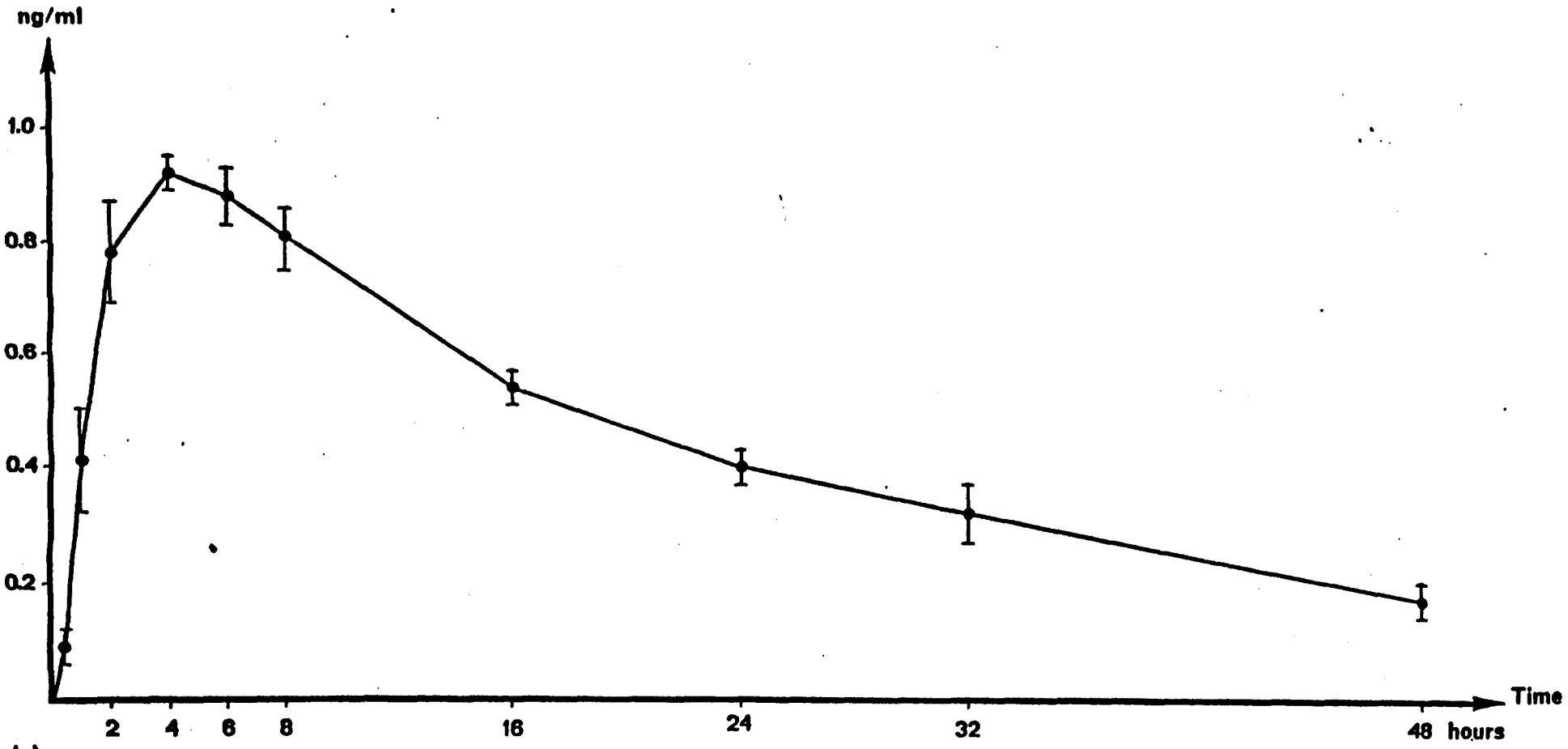
Table 11

FIGURE 1: Mean (± SEM) plasma concentrations (ng/ml) after oral administration of 1 mg [redacted] (n=8)



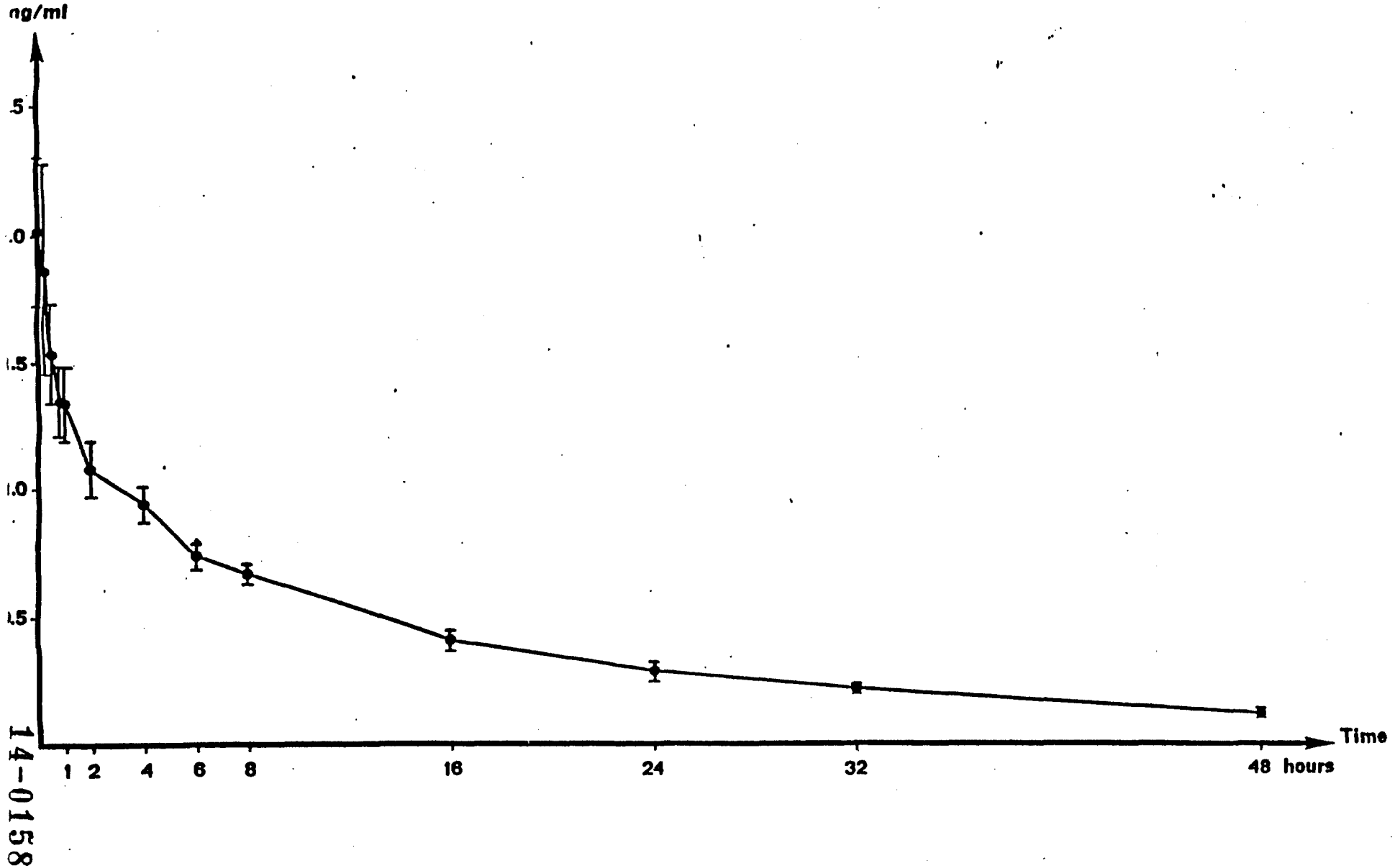
14-0159

FIGURE 2: Mean (±SEM) plasma concentrations (ng/ml) after oral administration of 2 mg [redacted] (n=8)



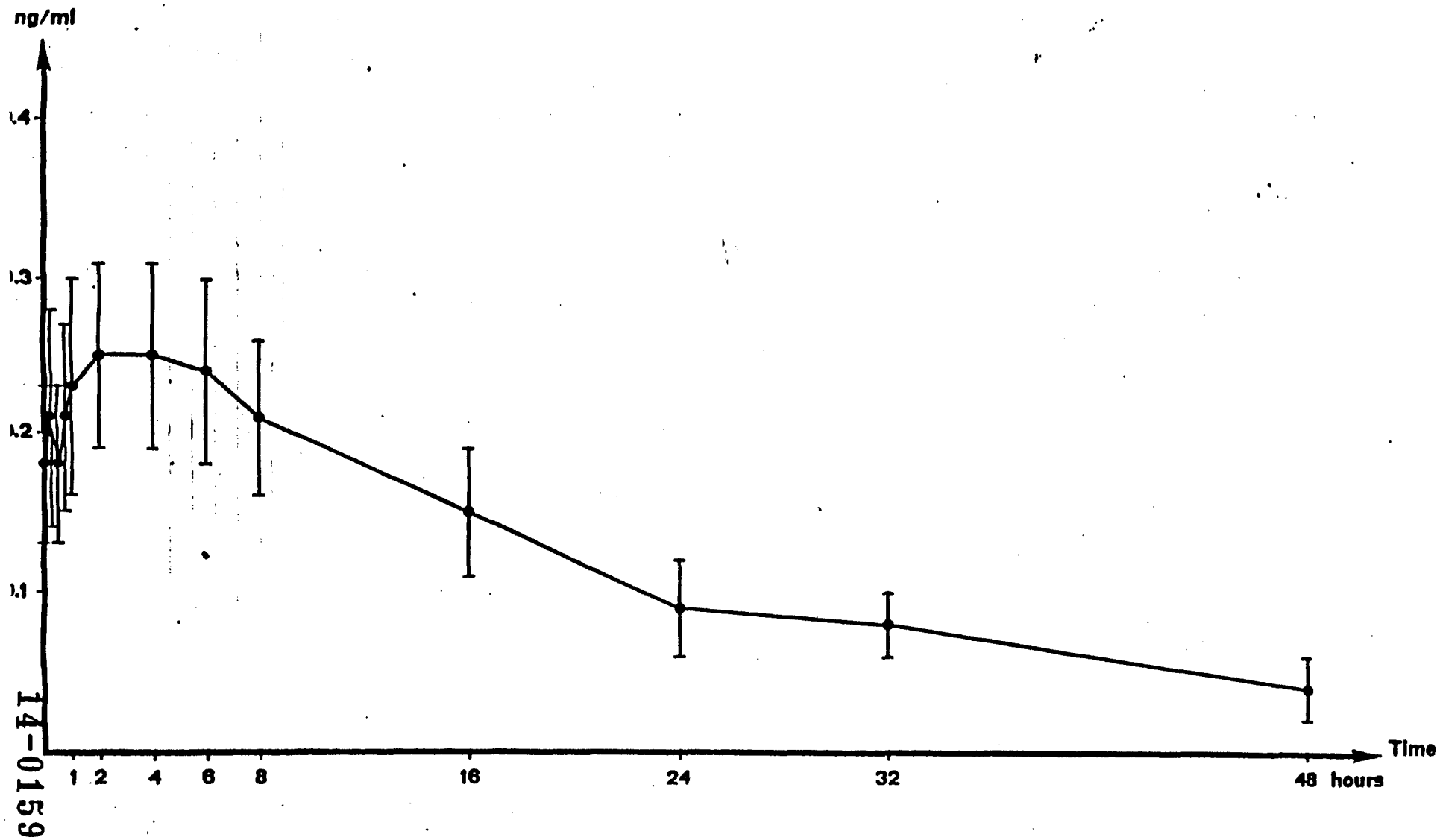
14-0157

FIGURE 3: Mean (±SEM) plasma concentrations (ng/ml) after intravenous injection of 1 mg [ ] (n=8)



14-0158

FIGURE 4: Mean (±SEM) plasma concentrations (ng/ml) after inhalation of 1 mg [ ] (n=8)



This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.

Memorandum for: Ketotifen Review Team

From: Andrea B. Weir, Ph.D. /S/ 6-30-99

Subject: Pharmacology/Toxicology Recommendations for the Ketotifen Label

Date: June 30, 1999

The Pharmacology/Toxicology recommendations for the ketotifen label are as follows:

[1] State that appropriate studies have not been conducted to assess the carcinogenic potential of ketotifen as opposed to including no information for carcinogenicity.

[2] Delete reference to retarded ossification of rabbit sternebrae

cc:
NDA 21-066
HFD-550/Div Files
HFD-550/MO/Dunbar
HFD-550/Dep Director/Chambers
HFD/550/PharmTox/ChenZ
HFD-550/PharmTox/Weir