CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-016

PHARMACOLOGY REVIEW

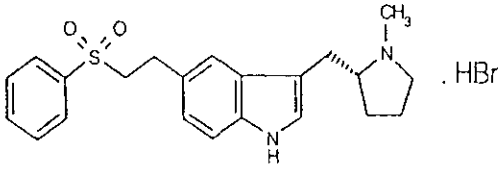
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: **eletriptan**, triptan, 5HT agonist, migraine
Reviewer Name: Robin Huff, Ph.D.
Division Name: Neuropharmacological Drug Products, HFD-120
Review Completion Date: June 25, 1999

IND/NDA Number: 21-016
Serial Number/Date/Type of Submission: 000/October 27, 1998/Original NDA
Information to Sponsor: Yes (X) No ( )
Sponsor (or agent): Pfizer
Manufacturer for Drug Substance: Pfizer

Drug:

Code Name: UK-116,044-04
Generic Name: eletriptan hydrobromide
Trade Name: Relpax
Chemical Name: (R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1*H*-indole hydrobromide
CAS Registry Number: 177834-92-3
Molecular Formula/Molecular Weight: $C_{22}H_{27}BrN_2O_2S$/463.43
Structure:



Relevant INDs/NDAs/DMFs: IND [redacted]

Drug Class: $5HT_{1B/D}$ agonist

Indication: migraine

Clinical Formulation: tablet

Route of Administration: oral

Proposed Clinical Use: MRDD of 2 x 80 mg, separated by > 2hr

Disclaimer – Some tables and graphs have been taken directly from the sponsor's submission and are so designated.

Pharmacology

Eletriptan was developed for the treatment of migraine on the basis of its high affinity (K_i's: 1 – 10 nM) and selectivity for 5HT1B, 1D and 1F receptors. Agonist activity has been demonstrated *in vitro* at both 5HT1B and 1D receptors; activity at 5HT1F receptors was not investigated, but may also contribute to the therapeutic action of the drug. The therapeutic action of triptans is generally attributed to two mechanisms, direct vasoconstriction of cerebral vasculature, mediated primarily by 5HT1B receptors, and blockade of trigeminal nerve-stimulated dural inflammation, mediated by 5HT1D and possibly 5HT1F receptors.

The sponsor's summary of the pharmacology studies conducted with eletriptan has been attached in Appendix A. A brief discussion of the studies that compared the vasoconstrictive effects of eletriptan and sumatriptan on coronary and cerebral arteries is warranted given the potential impact on labeling and marketing. The sponsor claims that eletriptan demonstrated greater selectivity than sumatriptan for constriction of cerebral arteries as compared to coronary arteries *in vitro*. These data are summarized in the first table below, from which it can be seen that although there were statistically significant differences in EC50's which resulted in a selectivity for cerebral vasoconstriction that is calculated to be 2.1 and 3.5 times greater for eletriptan than sumatriptan (dog and human data, respectively), in fact the differences in EC50's are not biologically meaningful (i.e., the differences between 69 and 150 nM and between 2000 and 890 nM are not biologically significant). *In vivo* data collected in dogs provides more convincing evidence of a slightly better cerebral artery vasoconstriction selectivity for eletriptan compared to sumatriptan. These data are summarized in the second table below and demonstrate a slightly greater separation of ED50's for reducing carotid artery blood flow and coronary artery diameter for eletriptan compared to sumatriptan The maximal effects were, however, similar for both drugs.

Vasoconstriction of Isolated Arteries *In Vitro*

Drug	EC50 in Dog Arteries (nM)		EC50 in Human Arteries (nM)	
	Basilar	Coronary	Meningeal	Coronary
eletriptan	69*	200	25	2000*
sumatriptan	150	210	39	890

*statistically different from sumatriptan

***In Vivo* Vasoconstriction in Dogs**

Drug	ED50 (μg/kg i.v.) for Reducing		Carotid Selectivity
	Carotid Blood Flow	Coronary Artery Diameter	
eletriptan	12* [10 – 15.5]	63* [37 – 107]	5.2*
sumatriptan	9 [7 - 11]	18 [11 – 31]	2.0

*statistically different from sumatriptan
95% confidence interval given in brackets

Absorption, Distribution, Metabolism and Excretion (ADME)

I. Pharmacokinetics

The pharmacokinetics of eletriptan were evaluated after a single administration to male CD-1 mice, Sprague-Dawley rats and Beagle dogs and female New Zealand White rabbits. Parameters are summarized in the table below. Toxicokinetic data collected within toxicology studies are evaluated with respect to human exposure within the review of each individual study.

Parameter	Mouse		Rat		Dog		Rabbit
	i.v.	oral	i.v.	oral	i.v.	oral	oral
Dose (mg/kg)	10	300	3	10	1	1	10
AUC (ng.h/ml)	1890	33700	456	193	577	292	37.4
Cmax (ng/ml)		9700		172		35	11.0
Tmax (hr)		0.25		0.5		1.0	1.0
$t_{1/2}\alpha$ (hr)	0.3						
$t_{1/2}\beta$ (hr)	3		1.4	2.0	3.9	4.8	2.6
Cl (ml/min/kg)	88		110		29		
Vd (l/kg)	10.3		10.9		7.9		
F (%)		60		13		51	

$AUC_{0\text{-}24hr}$ for oral mouse data, $AUC_{0\text{-}\infty}$ for all others

i.v. doses were bolus for rodents and 10 min infusions for dogs

Isomerization *in vivo* appears to be negligible because no S-enantiomer was detected in selected rat and dog samples (precisely which samples were evaluated was not specified).

II. Distribution

Distribution of radioactivity in four male (1 each at 0.1, 1, 24, and 96 hr) and two female (1 each at 1 and 24 hr) pigmented rats was determined following a 3 mg/kg i.v. dose of [^{14}C]eletriptan; distribution after oral dosing was not studied. Distribution was qualitatively similar in male and female rats. Distribution was rapid, with most tissue concentrations exceeding blood concentration at 0.1 hr; however, the concentration in brain at 0.1 hr was only 25% of the blood concentration. The kidney medulla, small intestine and bile contained high concentrations of radioactivity, suggesting both urinary and biliary excretion. By 1 hr after dosing, concentrations had diminished in most tissues except the retina and tissues involved in biliary excretion. By 24 hr, concentrations were generally < 2% of the 0.1 hr values, again except for the retina and tissues involved in excretion. By 96 hr, trace amounts of radioactivity were detectable in liver and large intestine, and a significant amount remained in the retina. The retainment of radioactivity in the retina ($t_{1/2}$ appears to be ~2 days based on limited data) suggests the binding of eletriptan and/or metabolites to melanin; however, binding to pigmented skin was notably less, with barely detectable amounts of radioactivity present by 24 hr.

In vitro protein binding of [^{14}C]eletriptan was consistent over the concentration range of 0.01 – 1 µg/ml, and averaged 62, 61, 76, 52, and 76% for mouse, rat, rabbit, dog and human plasma, respectively. The 1 µg/ml concentration is five times the Cmax associated with an 80 mg dose in humans. The report stated that the experiment was performed in triplicate, but it is not clear from this statement whether a single animal was the source of plasma for each species; therefore, it is not clear whether interindividual variability was assessed.

III. Metabolism

The metabolic profile of eletriptan was studied in rats, mice, rabbits and dogs. For all species, plasma was collected 1 hr after oral dosing of [^{14}C]eletriptan, and urine and feces were collected for 5 days. In all species there was evidence of extensive metabolism of eletriptan.

One hour after a 200 mg/kg dose, parent drug accounted for 59% of radioactivity in the plasma of male rats (n = 3), but only 23% of radioactivity in the plasma of female rats (n = 3). Four metabolites were present in the plasma of both males and females. Three of the metabolites each accounted for < 10% of the radioactivity; the fourth metabolite accounted for 26% of the radioactivity in males and 55% in females. In urine, total radioactivity accounted for 26% of the dose; parent drug accounted for 10% of the dose, and each of four metabolites accounted for <10%. In feces, total radioactivity accounted for 66% of the dose; parent drug accounted for 8% and 16% of the dose in males and females, respectively, two metabolites each accounted for 18 – 26% in both males and females, and another metabolite accounted for 17% in males and 7% in females. The presence of only 8 - 16% of the dose as parent in the feces likely indicates significant absorption, unless there is substantial metabolism of eletriptan along the gastrointestinal tract. In light of the apparently substantial absorption of eletriptan, the low 13% estimate of bioavailability in rats (see Pharmacokinetics section, above) suggests an extensive first pass effect in rats or nonlinear pharmacokinetics.

One hour after a 90 mg/kg dose, parent drug accounted for 40% of radioactivity in the plasma of mice (n = 3/s) Four metabolites were present in the plasma, one of which accounted for 39% of the dose, with each of the others accounting for < 10%. In urine, total radioactivity accounted for 14% of the dose; parent drug accounted for 6%, and each of four metabolites accounted for < 4%. In feces, total radioactivity accounted for 57% of the dose; parent drug accounted for 23% of the dose in males, but only 10% in females Three metabolites each accounted for 24, 4, and 8% of the dose in both males and females. Females produced an additional metabolite that accounted for 7% of the dose.

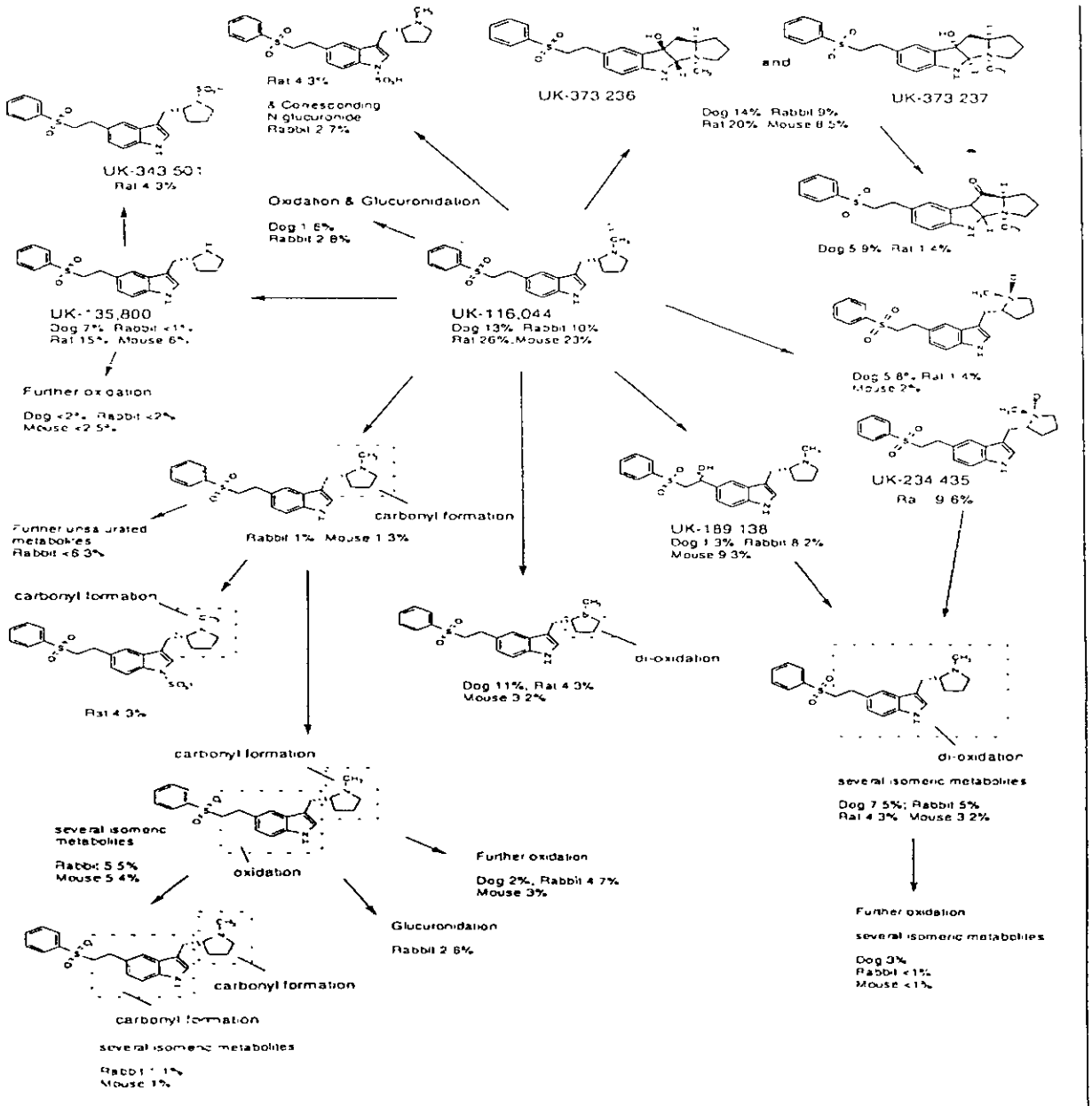
One hour after a 10 mg/kg dose, no parent drug was detectable in the plasma of rabbits (n = 3 F). Two metabolites accounted for 38 and 47% of the radioactivity, respectively. In urine, total radioactivity accounted for 32% of the dose; parent drug accounted for only 1%, and two metabolites accounted for 3 and 28%, respectively. In feces, total radioactivity accounted for 42% of the dose; parent drug accounted for 18% of the dose, and two metabolites accounted for 10 and 14%, respectively.

One hour after a 2.5 mg/kg dose, parent drug accounted for 23% of the radioactivity in the plasma of dogs (n = 2/s). Five metabolites were present in the plasma, three of which were poorly resolved and accounted for 70% of the radioactivity. In urine, total radioactivity accounted for 24% of the dose; parent drug accounted for 4% of the dose, and each of five metabolites accounted for < 9%. In feces, total radioactivity accounted for 77% of the dose; parent drug accounted for 18% of the dose, and four metabolites each accounted for 25, 16, 10 and 7%. As was found in other species, the presence of only 18% of the dose as parent in the feces likely indicates significant absorption of eletriptan.

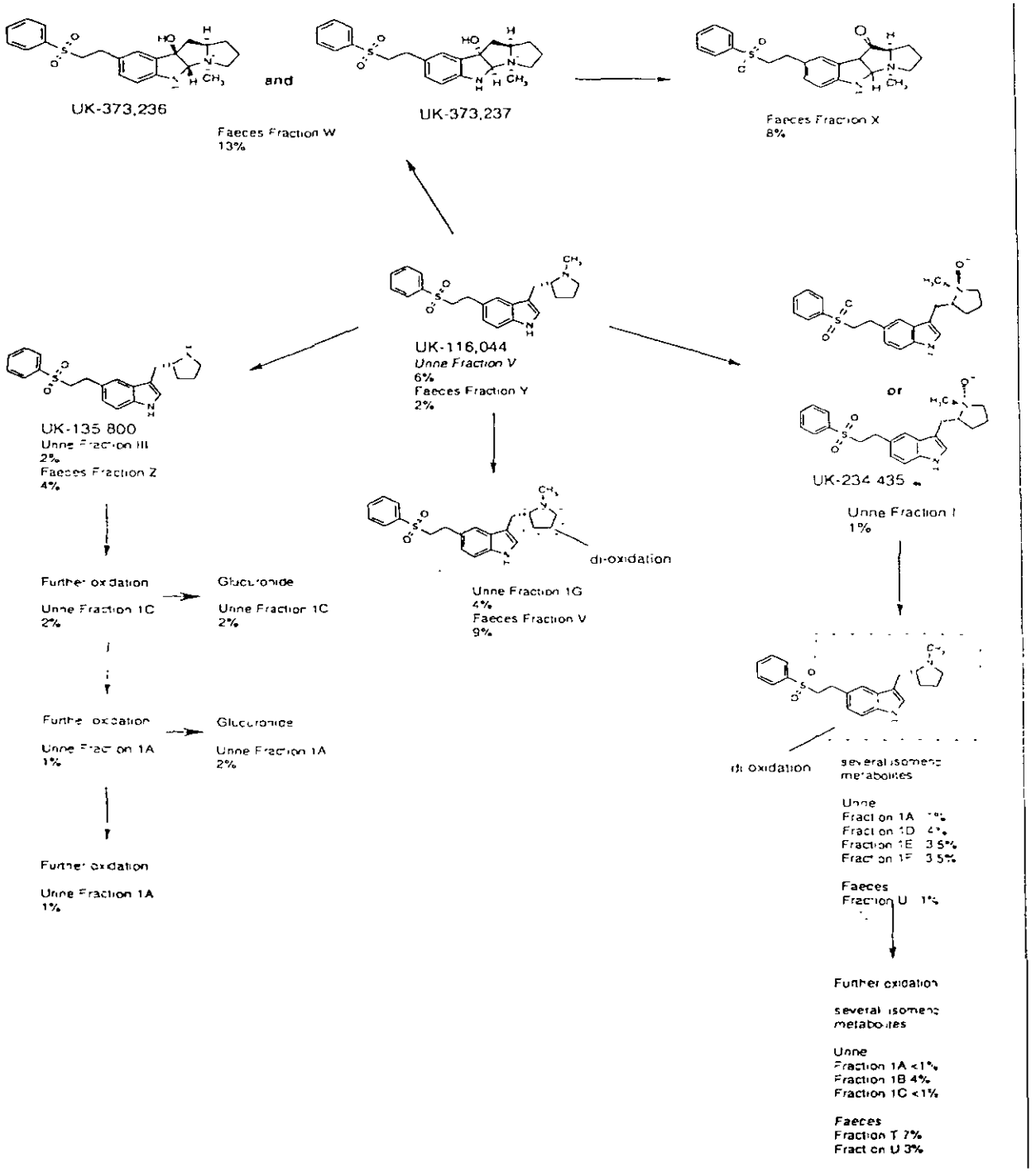
In the reports for the studies described above, the individual metabolites were not identified. However, in a separate study report, excreta samples from these studies were used to isolate and identify metabolites. Data were presented only as percent of total dose (presumably data from urine and feces were combined) and are summarized below in the sponsor-supplied

metabolism scheme. Six principal metabolic pathways are indicated, pyrrolidine N-demethylation, aliphatic hydroxylation β– to the phenyl sulphone group, pyrrolidine N-oxidation, tetracyclic quaternary ammonium formation, di-oxidation and carbonyl formation mainly on the pyrrolidine ring. The scheme indicates that most metabolic pathways are shared across species, with a few notable exceptions (e.g., pyrrolidine N-oxidation does not occur in the rabbit) The metabolic scheme proposed for humans is provided for comparison (n = 3 M, 30 mg). Human plasma collected 1 hr after a 30 mg oral dose contained parent drug and 3 metabolites; parent drug accounted for 30% of circulating radioactivity, the pyrrolidine N-oxide accounted for 23%, the pyrrolidine N-demethylation product accounted for 7%, and an unidentified fourth metabolite accounted for 35%. The N-oxide was found to be devoid of vasoconstrictive properties *in vitro*, whereas the N-desmethyl exhibited activity similar to that of eletriptan.

Proposed Metabolic Pathways for Eletriptan in Rat, Mouse, Rabbit and Dog



Proposed Metabolic Pathways for Eletriptan in Humans



When metabolism of eletriptan was investigated *in vitro*, parent drug was removed from mouse, rat, rabbit, dog and human microsomal preparations with $t_{1/2}$'s of > 120, 3, 8, 21, and 42 min, respectively. The range for the five human samples was 18 - 70 min. The rapid removal of eletriptan by rat microsomes supports the previously suggested extensive first pass effect in rats. Studies that address the specific P450 isozymes involved in the metabolism of eletriptan are evaluated in Dr. Rae Yuan's biopharmaceutics review.

IV. Excretion

After oral dosing of eletriptan, excretion was nearly complete within 48 hr in all species tested (72 hr for human feces). As tabulated below, the majority of drug-related material was excreted in the feces with the balance being excreted in the urine, except for humans in which excretion was equally divided between urine and feces. Data suggest that eletriptan and/or its metabolites undergo extensive biliary excretion. In cannulated rats, 53% of the dose was recovered in the bile within 2 hr of a 1 mg/kg i.v. dose, and the metabolite profile in excreta was similar after oral and intravenous dosing. The $t_{1/2}$ in dogs for elimination of radioactivity from plasma was 7.3 and 8.1 hr after oral and intravenous dosing, respectively; this parameter was not determined in other species.

Species	n	Dose	Percent of Dose Excreted in	
			Feces	Urine
Rat	3/s	200 mg/kg	71	28
Mouse	3/s	90 mg/kg	69	14
Rabbit	3 F	10 mg/kg	54	36
Dog	2/s	2.5 mg/kg	65	26
Human	3 M	30 mg	45	44

For species in which both sexes were evalutated, no sex-related differences in excretion pattern were observed; therefore, data from M and F have been combined. Slight differences in the excretion values reported here and those cited above in the metabolism section reflect that samples were pooled prior to being analyzed for metabolites.

APPEARS THIS WAY
ON ORIGINAL

Chronic Toxicology

I. Rats, 6 month oral (94044) GLP, QA
Pfizer (Amboise, France), conducted in 1994

Sprague-Dawley rats - 5, 15, 50 mg/kg p.o. gavage (batch R108)
20/s/gr (and 5/s/gr for toxicokinetics)

Mortality — 1 LD animal died immediately after dosing on day 166 and 2 MD animals were found dead on days 55 and 96. Additionally, 1 LD and 1 MD animal from the companion toxicokinetic study were found dead on days 60 and 130, respectively. Histopathology did not reveal a cause of death for any of the animals. There were no HD deaths, and it is not clear that the LD and MD deaths were treatment-related.

Clinical Signs — There were no treatment-related clinical signs. This suggests that a dose of at least 100 mg/kg should have been included, as was done in the 1 month study. Even at 100 mg/kg in the one month study (97075), toxicity was limited to increased liver weight (~20%) and thyroid follicular hypertrophy in F only. [It is unclear from dose range-finding studies what the MTD is in rats, although it is clear that 1000 mg/kg is lethal. On days 2 – 3 of a 5 day study, death occurred in 2/4 animals within 15 minutes of being given the HD of 400 mg/kg; both animals were found to have full stomachs and one was also found to have liquid (presumably test material) in the lower airway. The sponsor attributed the deaths to drug-induced inhibition of gastric motility that resulted in inhalation of rejected test solution; however, the presence of test material in the lung could also be indicative of a gavage error. On days 3 and 7 of a 14 day study in rats, 2/5 F (0/5 M) given 200 mg/kg died, but there was no obvious cause of death. Unlike the deaths that occurred at 400 mg/kg in the 5 day study, the deaths at 200 mg/kg were delayed ≥ 2.5 hr after dosing. In both of the range-finding studies, the incidences of dyspnea and decreased activity were such that animals other than those that died were affected, lending some support to the possibility that the deaths were treatment-related.]

The sponsor notes that cutaneous or subcutaneous masses were found in 1/40 controls and 4/40 HD animals.

Body Weight — From week 2 onward, MD and HD F weighed 4 - 7% more than controls. While there was no effect of treatment on food consumption, water consumption in HD F increased progressively from the second month to a final increase of 34% at the end of the study.

Eyes — Indirect ophthalmoscopy following mydriasis was performed prior to treatment and at the end of the study. There were no treatment-related findings.

Hematology — Parameters were measured after 2, 4, and 6 months. HD F had 2 - 4% decreases in RBC's relative to control, significant only at 6 months. Because no pretreatment measurements were made, it is possible that HD F began the study

with slightly lower values than controls. At 6 months, leukocytes were increased 17% in HD M, reflecting 70% increases in neutrophils and monocytes, and a 48% increase in large unstained cells. The number of HD M with neutrophil, monocyte, and large unstained cell counts that were greater than the highest control counts, were 3/20, 6/20, and 4/20, respectively, and histopathological examination revealed that some of these animals had skin abscesses that may have contributed to the leukocytosis. Neutrophils were transiently increased 59 and 46% in LD and HD F, respectively, at 2 months. Monocytes were increased 51 and 72% in LD and HD F at 6 months, and 48% in HD F at 4 months. Although 10/20 HD F had 6 month monocyte counts that were greater than the highest control count, only 3 of the 10 were more than 15% greater than the highest control value. Furthermore, the sponsor notes that means for the treated groups were within historical control range and that atypically low control values contributed to the apparent monocyte increase in the treated groups.

Clinical Chem — Parameters were measured after 2, 4, and 6 months. Cholesterol was increased up to 36% in MD and HD M and F throughout the study. Triglycerides were increased in F only, with increases being ~85% in HD F throughout the study and progressing to this extent in MD F by 6 months. There were 3 - 6% increases in calcium and protein in MD and HD animals, but few individual values exceeded the highest control values. Chloride concentrations were greatly increased in treated groups (*e.g.*, at 6 months the increase was 54% in HD M). The sponsor reports that the chloride concentrations are artifactually high because the bromide moiety of eletriptan causes analytical interference with the chloride assay.

Urinalysis — Parameters were measured after 2, 4, and 6 months. Urinary volume generally increased with both dose and time in F; the volume in HD F at 6 months was 73% greater than control. The volume increase may be responsible for the 0.5 - 0.6 pH unit decrease in urine of HD F.

Toxicokinetics — Blood samples were taken from satellite animals (5/sex) at 1, 3, 7, and 24 hr after the 139th dose. Tmax was 1 hr for all but 1 LD M. AUC and Cmax values are tabulated below. Exposure was approximately two times greater in F than M. The AUC's obtained in HD M and F were only 1.4 and 2.8 times, respectively, the 3000 ng.h/ml exposure achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr). The AUC's in rats were extrapolated from 1 hr rather than 0 hr, but based on the graphic representation of the data this would not be expected to significantly affect the AUC calculation. The Cmax's obtained in HD M and F were 3.6 and 5.7 times, respectively, the 200 ng/ml Cmax achieved in humans given an 80 mg dose.

Dose (mg/kg/day)	$AUC_{1\text{-}24hr}$ (ng.h/ml)		Cmax (ng/ml)	
	M	F	M	F
5	-	-	10	30
15	660	1320	200	350
50	4300	8370	720	1140

Organ Weights Liver weight was slightly increased in HD F; the relative increase was 14%. Testicular weights were decreased at all doses; the relative decreases were 8 - 12%. It is not possible to determine if ovary weights were decreased, as occurred in the 6 month dog study, because these data were not collected.

Pathology No gross pathology summary table was provided. The sponsor reports single cutaneous nodules on 4 HD M, 1 HD F and 1 MD F, and "minimal and diffuse pituitary enlargement" in 1 MD and 2 HD F. A complete battery of tissues from all control and HD animals underwent histopathological examination, as did thyroid, pituitary, liver, kidneys and testes in MD animals, and thyroid and testes in LD animals. Findings were limited to hemosiderosis in the spleen of 4/20 HD F (0 control) and an increased incidence of progressive chronic nephropathy in HD M (18/20 v. 12/20 control) and HD F (9/20 v. 2/20 control). The incidence of thrombosis in the heart doubled in HD F (11/20 v. 5/20 control), but was still less than the incidence in control M. The incidence of cysts in the glandular mucosa of the stomach increased in HD F (5/20 v. 1/20), but was still less than the incidence in control M.

II. **Dogs, 6 month oral** (94043) GLP, QA
Pfizer (Amboise, France), conducted in 1994

Beagle dogs - 1.25, 2 5, 5 mg/kg via capsules (batch R107)
4/s/gr

Note: Dosing was 0.63, 1.25, 2.5 mg/kg for the first 7 days in an effort to mitigate the cardiovascular effects (increased SBP and HR) that the sponsor claims were seen mainly during the first week of the 1 month tox study (1.25, 2.5, 5.0 mg/kg). Examination of data from the 1 month study indicates that SBP and HR were affected throughout the study, not just during week 1.

Mortality None

Clinical Signs Mydriasis occurred in all dogs except 1 LD animal. Mydriasis was first observed on day 1 for HD, day 8 for MD, and day 28 for LD animals. Onset was generally 3 hrs after dosing and dissipated by 24 hrs.

Body Weight There were no treatment-related effects.

Cardiovascular Parameters were measured prior to the study and on days 1, 8, 34, 75, 113 and 173 prior to dosing and ~1.5 hrs after dosing. At 1.5 hr after dosing heart rate was increased in all dose groups; mean increases were 23 - 33% at the LD, 23 - 58% at the MD, and 31 - 75% at the HD. Increases became noticeable by day 1 at the HD, day 8 at the MD, and day 34 at the LD animals, and persisted throughout the study (see sponsor-supplied table below). Throughout the study systolic arterial BP was increased after dosing; mean increases were as great as 32% in HD animals and 23% in MD animals. A 21% increase occurred in LD animals on day 34, but there were no notable increases in LD animals at other time points. No reason is provided for the exclusion of several data

measurements of "> 250 mm Hg" on day 34 that would have resulted in greater mean BP increases than reported for all dose groups. One such measurement was also excluded from the control mean on day 34 and the HD mean on day 113.

P wave duration was increased 7 4 - 9.8 msec in HD animals after dosing on day 8 and all subsequent test days (typical P wave duration ~45 msec). PQ and QRS intervals were not affected by treatment; however, QT interval in MD and HD animals was decreased after dosing. Mean decreases of up to 29 msec were seen throughout the study (typical QT interval ~200 msec). From day 1, P-wave amplitude was increased following treatment in MD and HD animals. Mean increases of up to 0 094 and 0.042 mV were observed in HD and MD animals, respectively (typical P-wave amplitude ~0.205 mV). The sponsor indicates that the ECG changes were likely consequent to the increase in heart rate. It is noted that the incidence of T-wave polarity reversal was increased with dose.

Percent Changes in Heart Rate Relative to Pre-Dose Values

Dose[a] (mg/kg)	Day 1	Day 8	Day 34	Day 75	Day 113	Day 173
Control	2	0	-11	-3	2	-16
1.25	1	9	23 **	24 *	33 *	24 **
2 5	14	26 **	36 ***	38 ***	58 ***	23 ***
5.0	31 ***	47 ***	54 ***	76 ***	75 ***	62 ***

[a] Animals received 0, 0.63, 1.25 or 2.5 mg/kg during the first week then 0, 1.25, 2.5 or 5 mg/kg.
*, **, *** = statistically significant at p = 0.05, 0.01 and 0.001 respectively, relative to control values.

Eyes — Light reflexes were examined and indirect ophthalmoscopy following mydriasis was performed prior to treatment and on days 161 - 162. The sponsor reports that on day 161 all HD animals exhibited slight miosis prior to dosing, but this is not indicated in the data. Perhaps the sponsor actually meant mydriasis, as described under clinical signs.

Hematology — Parameters were determined prior to treatment and after 2, 4, and 6 months. Slight decreases relative to control of 7 - 17% in RBC, Hb, and HCT were observed at 2 months in all drug-treated F groups (decreases were slightly less when calculated relative to pretreatment values).

Clinical Chem — Parameters were determined prior to treatment and after 2, 4, and 6 months. At all time points ALP was increased relative to control in all drug-treated M groups (up to 46% at the MD and HD, but half of the difference at the HD was present prior to treatment). However, increases were notably higher than pretreatment values for only the LD group (mean increases were 55, 42, and 34% at 2, 4 and6 months, respectively, with one animal displaying 155, 116,

and 119% increases). LD F showed an 86% increase in ALP relative to pretreatment, with one animal having a 236% increase; the increase occurred at 2 months, but abated by 4 months. In drug-treated males triglycerides were increased 21 - 59% in a dose-independent fashion at all time points.

Urinalysis — Parameters were determined prior to treatment and at the end of the study. There were no treatment-related changes.

Toxicokinetics — Blood samples were taken at 1, 3, 7, and 24 hrs after the 146th dose. Tmax was achieved at 1 - 3 hr, and plasma drug concentration was generally below the level of detection (0.008 µg/ml) by 24 hrs. AUC values were fairly dose-proportional as indicated in the table below. Pharmacokinetic parameters calculated in this study are similar to those determined in the 1 month study The exposure achieved at the HD is less than the 3000 ng.h/ml $AUC_{0-\infty}$ achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr). The AUC comparison is made with the caveat that the dog AUC was calculated for 1 – 7 hr only; however, the graphic presentation of the data indicates that this time frame appears to account for more than half of the total exposure. The Cmax obtained at the HD is twice the 200 ng/ml Cmax achieved in humans given an 80 mg dose.

Dose (mg/kg/day)	$AUC_{1\text{-}7hr}$ (ng.h/ml)	Cmax (ng/ml)
1.25	204	54
2.5	653	155
5.0	1680	413

Organ Weights — Mean absolute ovary weight was decreased 47, 23, and 37% in LD, MD, and HD F, respectively; decreases in relative weight were similar. These decreases may merely reflect individual variability because all but one weight fell well within the historical control range.

Pathology — Cardiac fibrosis, which was seen in 2/3 M given 5 mg/kg in the 1 month study and in 1/2 F given 7.5 mg/kg in the 2 week study, was not observed in this study. In the brain, perivascular cuffing was noted in 2/8 HD animals and granulomatous inflammation was observed in 1/8 HD animals. In the lung, subpleural inflammation (2/8 LD, 1/8 MD, 4/8 HD v. 0/8 C), broncho-pneumonia (4/8 LD, 2/8 MD, 1/8 HD v. 0/8 C), and granuloma (4/8 LD, 1/8 MD v. 0/8 C) occurred more frequently in treated than control animals, but were not dose-related. Cysts were present in the thymus of treated animals more frequently than in controls (3/8 LD, 4/8 HD v. 0/8 C), but this was also not dose-related. Also not related to dose was glandular dilation in the prostate of 2/4 LD and 1/4 HD M and chronic inflammation of the prostate in 1/4 LD and 1/4 MD M.

Two MD and 1 HD animal had multifocal, depressed, red areas up to 10 mm in diameter on the mucosal surface of the fundic region of the stomach. Microscopically, one of the MD animals and the HD animal had deep

ulcerations of the fundic mucosa, with granulation tissue at the base indicative of chronic insult. The sponsor postulates that localized vasoconstriction produced at sites of concentrated drug release may have caused the lesions. The other affected MD animal had an area of superficial acute inflammation in the fundic mucosa.

III. Dogs, 12 month oral (96024) GLP, QA
Pfizer (Amboise, France), conducted in 1996-97

Beagle dogs – 0.6, 1.25, 4 mg/kg via tablets (substance batches R112 and R203)
4/s/gr (and 4/s C and HD for gastroscopy at 0, 3. 6, 9, and 12 months)

Note: Dosing was 0.3, 0.6, 2 mg/kg for the first 7 days in an effort to mitigate the cardiovascular effects (increased SBP and HR) that the sponsor claims were seen mainly during the first week of the 1 month tox study at doses of 2.5 and 5 mg/kg. Examination of data from the 1 month study indicates that SBP and HR were affected throughout the study, not just during week 1

Mortality — None

Clinical Signs — Mydriasis was observed sporadically at the MD and daily at the HD for the first 10 months of the study. During the last 2 months of the study, mydriasis became sporadic at the HD. Mydriasis resolved each day prior to dosing on the subsequent day.

Body Weight — There were no treatment-related effects.

Cardiovascular — Parameters were measured prior to the study and during weeks 1, 2, 12, 28 and 50 prior to dosing and ~1.5 hr after dosing. HR was increased after dosing from week 2 onward at the HD. The mean increase was 33%, but individuals experienced increases of up to 72%. Unlike in the 6 month study, SBP was not increased.

Although the sponsor reports no ECG changes, QT interval was slightly decreased (6 - 11%) throughout the study after administration of the HD, which likely reflects the increase in HR observed at this dose. Also, 4/8 HD animals experienced 18 – 47% increases in P-wave duration after dosing; in 3 of 4 the increase was consistently observed throughout the study. Five HD animals experienced 40 - 83% increases in P-wave amplitude after dosing; the changes were first observed at week 12 or later, and recurred in 3 of 5 animals. The sponsor also reports increased T-wave amplitude in 1/8 MD and 2/8 HD animals relative to pre-trial values, but the actual T-wave data were not provided. In one of the HD animals the increased T-wave caused the T/R ratio to increase above the ULN of 0.33 throughout the entire study (both before and after dosing on any given day).

Gastroscopy — Gastroscopy was performed at 3. 6, 9 and 12 months in 4/s satellite controls and 4/s satellite HD animals. (Presumably gastroscopy was performed because there was histopathological evidence of gastric irritation in a few animals in the

6 month study.) Generally the incidence of small red spots, located primarily in the greater curvature, was greater in the treated group, but there was no evidence of blood or erosion, and no histopathological correlates.

Group	Incidence of Red Spots at Month			
	3	6	9	12
Control	0/8	1/8	1/8	4/8
HD	5/8	7/8	4/8	6/8

Eyes — Light reflexes were examined and indirect ophthalmoscopy following mydriasis was performed prior to treatment and at 6 and 12 months. At 6 months, mydriasis was observed in HD animals 1 hour after dosing, but mydriasis was not observed at 12 months.

Hematology — Parameters were measured prior to treatment and at 3, 6, 9 and 12 months. One HD M experienced an 80% decrease in PLT at 3 months, relative to both control and pretreatment values; at 12 months PLT remained decreased 50%. Prothrombin time was slightly elevated in this dog to 7.2, 7.0, 7.2, and 6.8 sec at 3, 6, 9 and 12 months, respectively, versus mean control values of 6.2 – 6.4 and a pretreatment value of 6.5 sec. This animal also experienced slight decreases in RBC, Hb and HCT throughout the study; decreases were generally 8 – 16% relative to both control and pretreatment values.

Clinical Chem — Parameters were measured prior to treatment and at 3, 6, 9 and 12 months. There were no treatment-related effects.

Urinalysis — Parameters were measured at 6 and 12 months. There were no treatment-related findings.

Toxicokinetics — Samples were collected on days 27 and 342 at 1, 3, 7 and 24 hr after dosing. Kinetics were similar in M and F, and did not change over time. Tmax was 1 – 3 hr. Mean Cmax and AUC data are summarized in the following table. The exposure achieved at the HD is less than the 3000 ng.h/ml $AUC_{0-\infty}$ achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr). The AUC comparison is made with the caveat that the dog AUC was calculated for 1 – 7 hr only; however, the graphic presentation of the data indicates that this time frame appears to account for more than half of the total exposure. The Cmax obtained at the HD is similar to the 200 ng/ml Cmax achieved in humans given an 80 mg dose.

Dose (mg/kg/day)	AUC_{1-7hr} (ng.h/ml)	Cmax (ng/ml)
0.6	103	24
1.25	196	50
4	1250	273

Organ Weights There were no treatment-related effects. Unlike in the 6 month study, ovary weight was not decreased, further supporting the hypothesis that the decrease observed in the 6 month study merely reflected individual variability.

Pathology Although cardiac fibrosis was observed in 2/3 M given 5 mg/kg in the 1 month study and in 1/2 F given 7.5 mg/kg in the 2 week study, it was not observed in either this 1 year study or the 6 month study. Perivascular cuffing, which was observed in 2/8 dogs given 5 mg/kg in the 6 month study, was observed in 1/8 LD and 2/8 MD dogs, but no HD dogs in this 1 year study; thus, it appears not to be treatment-related. There was no notable pathology in lung, prostate, thymus or stomach; these organs were affected in treated animals in the 6 month study, but not in a dose-related manner. In summary, no target organs were identified in this study.

Reproductive Toxicology

I. Rat Fertility Study (94073) GLP, QA
Pfizer (Amboise, France), conducted in 1994

Sprague-Dawley rats – 5, 15, 50 mg/kg p.o. gavage (batch R108)
20/s/gr

Males were dosed for 9 weeks prior to mating, throughout mating and until termination of the females. Females were dosed for 2 weeks prior to mating, throughout mating and through GD6. C-sections were performed on GD20. Clinical signs were limited to transient salivation in MD and HD M and F. Body weight and food consumption were unaffected by treatment. Mating and fertility indices were unaffected by treatment (mating - 100% for all groups; fertility - 90. 95. 100. 100% for C, LD, MD, HD, respectively). Corpora lutea number, implantation site number, litter size and fetal viability were also unaffected by treatment. External fetal abnormalities were limited to microphthalmia in one control fetus, filamentous tail in one LD F and umbilical hernia in one HD fetus.

In light of the lack of reproductive or general toxicity, the doses selected for this study were too low. As justification for dose selection the sponsor cites the decreased BW gain observed at 100 mg/kg in the rat embryofetal development study (see below) and the thyroid follicular hypertrophy observed at 100 mg/kg in a 1 month general toxicity study (97075). The latter effect does not define an MTD and, therefore, should not be used to limit dosing. The BW gain deficit observed in the embryofetal development study is likely specific to the pregnancy status of the females during dosing, as it did not occur in the 1 month general toxicology study. Toxicokinetic data were not collected in the fertility study, but results generated in the 6 month general toxicology study indicate that AUC's in M and F rats given 50 mg/kg are only 1.4 and 2.8 times, respectively, that achieved in humans given the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr).

II. Rat Embyofetal Development Study (93061/62) GLP, QA
Pfizer (Amboise, France), conducted in 1993

Sprague Dawley rats - 10, 30, 100 mg/kg p.o. gavage (batch R7)
20 F/gr (and 5F/gr for toxicokinetics)

Rats were dosed throughout organogenesis, GD6 - 17; C-sections were performed on GD20. One HD F was killed on GD8 after exhibiting dyspnea, prostration and piloerection subsequent to a suspected gavage error on GD7. One HD F and 1 control were found to have only dead implants upon examination on GD20, and 1 HD F was found not to be pregnant. Salivation was observed immediately after dosing in MD and HD dams. BW gain during the treatment period was 14 and 26% less in MD and HD dams, respectively, than in controls. The decrease in BW gain was reflected in reduced food consumption measured on GD9, which was the only day during treatment when food consumption was measured, and resulted in GD20 BW's for MD and HD dams that were 4 and 6% less than control, respectively.

Preimplantation loss was increased in MD and HD dams as a result of large losses in 2 dams from each of these groups, but the increase is not likely treatment-related, given that implantation should have occurred prior to treatment initiation on GD6 (mean losses were 7.2, 16.0, and 12 8% in C, MD, and HD, respectively - percentages vary slightly from those stated by the sponsor because the sponsor did not calculate on a per litter basis). Other reproductive parameters were not affected.

Fetal weight was decreased 6 and 4% in HD M and F fetuses, respectively (the decrease in F fetal weight was not statistically significant). The number of HD fetuses (litters) with minor vertebral alterations was 11 (8) versus 3 (3) in controls, and the number exhibiting minor sternebral alterations was 4 (3) versus 1 (1) in controls. The percentages of fetuses displaying delayed ossification of vertebra and metacarpi doubled at the HD, but was similar to or less than historical control means. There was delayed ossification of the skull in a few HD fetuses, but the percentage was similar to historical control values.

Plasma concentrations of eletriptan were determined in 5 satellite F/gr on GD17 prior to dosing and at 1, 3, and 7 hr after dosing. After the 7 hr sampling, amniotic fluid and fetuses were collected for determination of eletriptan concentrations Results are tabulated below. The $AUC_{0\text{-}7hr}$ achieved at the HD is 2.4 times the 3000 ng.h/ml $AUC_{0-\infty}$ achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr). This comparison underestimates the rat/human AUC ratio because the rat AUC was calculated for 0 – 7 hr only and the graphic presentation of the data indicates that significant exposure may occur after 7 hr (furthermore, 280 ng/ml was still detected in the HD group prior to dosing). The Cmax obtained at the HD is 6.7 times the 200 ng/ml Cmax achieved in humans given an 80 mg dose. The HD of 100 mg/kg approximates an MTD based on the 26% decrease in maternal BW gain observed during the treatment period. In a dose range-finding experiment, 150 mg/kg produced even greater detriments in BW gain (44%) and a 16% decrease in fetal weight.

Dose (mg/kg)	Cmax* (ng/ml)	$AUC_{0\text{-}7hr}$ (ng.h/ml)	C_{fetal} (ng/g)	$C_{amniotic\ fluid}$ (ng/ml)
10	261	892	97	26
30	740	3120	570	147
100	1340	7340	2210	426

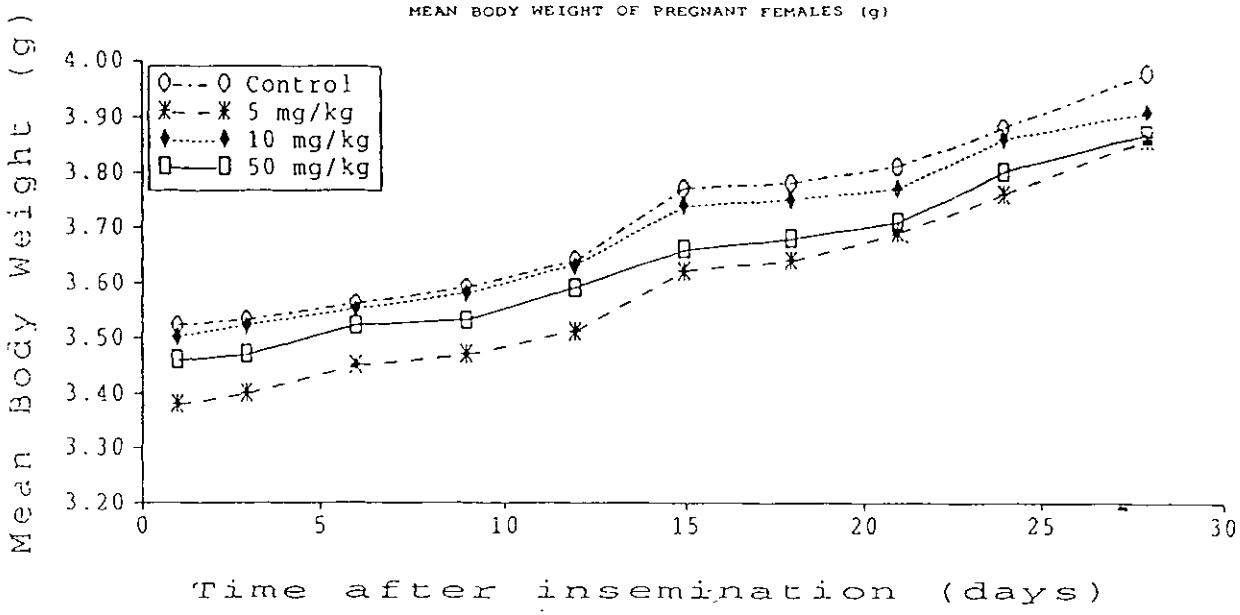
*Cmax occurred at 1 hr.

III. Rabbit Embryofetal Development Study (93059/60) GLP, QA
Pfizer (Amboise, France), conducted in 1993

New Zealand White rabbits - 5, 10, 50 mg/kg p.o. gavage (batch R7)
20 F/gr (and 4 LD F for toxicokinetics)

Rabbits were dosed throughout organogenesis, GD6 - 20; C-sections were performed on GD28. One control died 15 min after treatment on GD11, which suggests accidental intratracheal dosing. One MD F aborted on GD20, and 1 LD and 3 HD F were not pregnant. There were no treatment-related clinical signs; however, in a dose-ranging study, 100 mg/kg caused the death of 3/7 pregnant rabbits as well as notable decrements in BW gain. As of GD15 there was a slight decrease in BW gain at the HD such that the BW adjusted for GD6 was 2% less than control, which is of doubtful biological significance (see sponsor-supplied figure

below). Food consumption was slightly decreased (7%) at the HD on GD9, but not GD17. There was no treatment effect on reproductive parameters (corpora lutea, implantation sites, viable fetuses).



Fetal BW was decreased 7% at the HD. There were no major anomalies in the 132 control fetuses. The major anomaly of scoliosis was observed in 1 LD fetus; the sponsor reports the maximum background incidence of scoliosis to be 1/18 litters. Gastroschisis was observed in 2/138 (1/19) LD, 1/139 (1/19) MD, and 1/135 (1/17) HD fetuses (litters); the sponsor reports the historical control incidence to be 1/73 litters. The mother of the affected HD fetus did not gain weight from GD6 - 15 and the affected fetus weighed 24 47 g, less than the group mean of 32.16 g, suggesting that maternal effects may have contributed to the anomaly in the HD fetus. One of the LD fetuses that exhibited gastroschisis also displayed cardiac defects consisting of transposition of the great vessels, a right-sided descending aorta, deviation of the inferior vena cava and ventricular septal defect; the 20.66 g BW of this fetus was notably less than the group mean of 33.03 g. The sponsor states that "gastroschisis in the rabbit is often associated with defects of the heart and lungs," citing Palmer, 1968. One MD fetus exhibited ventricular septal defect.

Visceral variants included an increased incidence of vena cava deviation in all treated groups (3/132 [2/19] C, 8/138 [8/19] LD, 5/139 [4/19] MD, and 7/135 [5/17] HD fetuses [litters]); no historical control data were provided for this deviation. The incidence of another visceral variant, bilobed gall bladder, was increased at the HD (7/135 [4/17] HD v. 2/132 [2/19] control fetuses [litters]), but was within the historical control range of 0 - 10% of fetuses/33% of litters. Skeletal anomalies included the one LD fetus with scoliosis, and an increased incidence of fused sternebrae at all doses (0/132 [0/19] C, 8/138 [6/19] LD, 4/139 [3/19] MD, and 2/135 [2/17] HD fetuses [litters]).

Blood was collected from the four satellite 5 mg/kg rabbits 1, 3, and 7 hr after dosing on GD20. The mean plasma concentration of eletriptan at 1 hr was 8 ng/ml, and at 3 hr was at or below the 5 ng/ml level of detection. At 7 hr, eletriptan was not detected in plasma, amniotic

pups at birth and during lactation were monitored. The F_0 dams were necropsied at weaning (PPD 21).

On PPD 0, the number of pups were counted (dead and alive) and sexed. Pups were weighed individually on PPDs 1, 4, 14 and 21, then weekly thereafter. Dead pups were viscerally examined. On PPD 4, litters were culled to 4 pups/sex/litter. One culled pup/sex/litter was examined at necropsy for visceral anomalies.

Before weaning, F_1 pups were assessed for surface-righting and air-righting reflexes, appearance of superior incisors and opening of the palpebral fissures. After weaning, vaginal opening and presence of the prepucial fissure were examined. An ophthalmological exam was performed around PPD 22. In addition, pups were examined using a spontaneous motor activity test and a functional observational battery.

At about 12 weeks of age, 2 rats/sex/liter were retained for the study of reproductive function (Study no. 96017). "The other rats were euthanized and 10 pups/sex/group were necropsied."

Adult F_1 rats were weighed weekly and mated when about 3.5 months old. During the mating, male and female pairs were caged each night for 2 weeks. Vaginal smears were checked each morning during the mating period for presence of sperm or stage of the estrous cycle. Inseminated females were housed individually.

F_1 females were weighed on GDs 1, 3, 6, 9, 12, 15, 18 and 20, then on PPDs 1 and 4. The number of F_2 pups (dead and alive) and external anomalies were recorded. Viable pups were counted and sexed daily until PPD 4. The mean body weight of male and female pups from each litter was determined. Dead pups were necropsied and examined for visceral anomalies.

The F_2 pups and F_1 females were sacrificed on PPD 4. Ten pups/sex/group were examined macroscopically and "anomalies of mothers were sampled and kept in fixative".

Results, F_0 Females:

Mortality: In control 1 death (on PPD 4), at low dose 3 death (on GD 23, PPD 4 and 5) at mid dose 1 death (on PPD 4); causes of death not stated but apparently not compound-related.

Compound Related Effects

Clinical Signs: At high dose, salivation which lasted around 5 minutes following treatment, between GD 10 and PPD 21.

Body Weight: Sponsor's tables 3 and 5 which follow summarize mean body weights and mean body weight differences from control, with statistical analyses adjusted to GD 1 (even though treatment began on GD 6). On June 9, 1999, we consulted with Dr. Roswitha Kelly, statistician in HFD-710, because the differences between mean body weights of high dose and control groups were small and were based on adjusting to GD 1 (before treatment was initiated) instead of adjusting to GD 6, the day that treatment was initiated. Dr. Kelly confirmed that the sponsor's statistical analyses, based on mean body weight differences and adjusted to GD 1, was valid. At the high dose, there was a decrease in mean body weight gain between GD 6 – 9 such that body weights were significantly less than control throughout gestation and lactation. However,

body weights at the high dose were only 3 – 4% less than control. At the mid dose, there was a small decrease in body weight which was limited only to PPD 17 and PPD 21.

Table 3 - Covariance analyses of mean body weight of pregnant F_0 females with viable pups

15-JUN-98

COVARIANCE ANALYSIS OF PREGNANT FEMALE WEIGHTS (IN GRAMS)

PROTOCOL: 96016 COMPOUND: UK-116,044
SPECIES : RAT STUDY OF: STUDY II

	GROUP	N OF PREGNANT FEMALES	MEAN WEIGHT		DIFFERENCE FROM CONTROL	SIGNIFICANCE
DAY: 1	CONTROL	26	256.4	UNADJUSTED		
	5 MG/KG	26	248.8		-7.7	N.S.
	15 MG/KG	28	255.8		-0.7	N.S.
	50 MG/KG	27	251.0		-5.4	N.S.
DAY: 3	CONTROL	28	264.3	ADJUSTED FOR DAY: 1		
	5 MG/KG	26	267.0		2.8	P<0.05
	15 MG/KG	28	266.4		2.2	N.S.
	50 MG/KG	27	265.1		0.8	N.S.
DAY: 6	CONTROL	28	276.6	ADJUSTED FOR DAY 1		
	5 MG/KG	26	278.4		1.8	N.S.
	15 MG/KG	28	278.2		1.6	N.S.
	50 MG/KG	27	277.6		1.0	N.S.
DAY: 9	CONTROL	28	289.5	ADJUSTED FOR DAY 1		
	5 MG/KG	26	290.2		0.7	N.S.
	15 MG/KG	28	288.0		-1.5	N.S.
	50 MG/KG	27	280.6		-8.9	P<0.01
DAY: 12	CONTROL	28	305.8	ADJUSTED FOR DAY 1		
	5 MG/KG	26	304.7		-1.1	N.S.
	15 MG/KG	28	304.0		-1.8	N.S.
	50 MG/KG	27	295.7		-10.1	P<0.01
DAY: 15	CONTROL	28	323.3	ADJUSTED FOR DAY: 1		
	5 MG/KG	26	321.1		-2.2	N.S.
	15 MG/KG	28	321.4		-2.0	N.S.
	50 MG/KG	27	309.1		-14.2	P<0.01
DAY 18	CONTROL	28	360.3	ADJUSTED FOR DAY 1		
	5 MG/KG	26	355.8		-4.5	N.S.
	15 MG/KG	28	357.1		-3.2	N.S.
	50 MG/KG	27	314.0		-16.3	P<0.01
DAY 20	CONTROL	28	387.1	ADJUSTED FOR DAY. 1		
	5 MG/KG	26	379.3		-7.8	N.S.
	15 MG/KG	28	384.1		-3.0	N.S.
	50 MG/KG	27	371.4		-15.7	P<0.01

Table 5 - Covariance analyses of mean body weight of lactating F_0 females

Day p.p.	Group	Adjusted for day	N	Mean	Adjusted mean	Stderr	Linear trend p value
1	control	Not adjusted	28	291.5			
	5 mg/kg		26	289.4			
	15 mg/kg		28	290.0			
	50 mg/kg		27	283.2			NS
4	control	1 p p	28		305.9	1.70	
	5 mg/kg		26		305.5	1.76	
	15 mg/kg		28		303.8	1.70	
	50 mg/kg		27		301.6	1.74	NS
7	control	1 p p	27		312.4	2.28	
	5 mg/kg		24		308.8	2.42	
	15 mg/kg		27		309.6	2.29	-
	50 mg/kg		27		303.7	2.30	0.016 (*)
10	control	1 p p.	27		329.9	2.61	
	5 mg/kg		24		327.3	2.77	
	15 mg/kg		27		322.9	2.61	-
	50 mg/kg		27		319.0	2.63	0.0021 (**)
14	control	1 p p	27		336.5	3.09	
	5 mg/kg		24		336.2	3.28	
	15 mg/kg		27		332.2	3.10	-
	50 mg/kg		27		326.0	3.12	0.013 (*)
17	control	1 p p	27		341.4	2.94	
	5 mg/kg		24		339.2	3.12	-
	15 mg/kg		27		333.4	2.94	0.017 (*)
	50 mg/kg		27		332.9	2.96	0.014 (*)
21	control	1 p p	27		332.6	2.65	
	5 mg/kg		24		333.9	2.81	
	15 mg/kg		27		324.9	2.66	0.035 (*)
	50 mg/kg		27		322.3	2.68	0.018 (*)

NS. not significant at the 5% level
*. p≤0.05. **. p≤0.01

Reproduction Parameters: The data as originally presented and statistically analyzed in Table 7 is based on total numbers of dead and viable fetuses and pups/group. The sponsor was asked to reorganize Table 7 and to have the data and statistics based on fetuses and pups/litter in each group. Both the original and revised tables are shown below. The revised table indicates that there was a slight increase in *in-utero* deaths per litter [(P<0.05) including dead pups at birth] There was also an increase in post-implantation loss/litter at low (P<0.01) and high (P<0.05) doses, corresponding to slightly lower mean numbers of viable pups per litter (n.s.) in these two groups.

Table 7 - Summary reproduction data of F_0 females

19-SEP-97 10:05:17
PROTOCOL 96016 UK-116,044-04 RAT
REPRODUCTION STUDY II (F0/F1 GENERATION)

	RESULTS			
REPRODUCTIVE VARIABLES	CONTROL	5 MG/KG	15 MG/KG	50 MG/KG
PREGNANCY RATE (%)	28/ 28 (100.0)	27/ 28 (96.4)	28/ 28 (100.0)	28/ 28 (100.0)
LENGTH OF GESTAT. MEAN ± S.D.	21.4 ± 0.49	21.5 ± 0.51	21.5 ± 0.51	21.4 ± 0.51
VIABLE PUPS AT BIRTH (%)	405/415 (97.6)	352/354 (99.4)	404/412 (98.1)	370/386 (95.9)
DEAD IN UTERO RATE (%) (POST IMPLANTION LOSS)	14/429 (3.3)	27/381** (7.1)	15/427 (3.5)	21/407* (5.2)
MEAN LITTER SIZE ± S.D	14.5 ± 2.8	13.5 ± 2.4	14.4 ± 2.1	13.7 ± 2.1
NUMBER OF VIABLE LITTERS AT BIRTH	28	26	28	27
MEAN NUMBER OF IMPLANTATION SITES ± S.D	15.3 ± 2.7	14.7 ± 2.4	15.3 ± 2.1	15.1 ± 1.7

*, ** statistically significant at p = 0.05 and p = 0.01 respectively

Supplementary reproduction data for F_0 females

	Control	5 mg/kg	15 mg/kg	50 mg/kg
Mean number of viable pups per litter at birth (Mean ± S.D.)	14.5 ± 2.8	13.5 ± 2.4	14.4 ± 2.1	13.7 ± 2.1
Mean number of dead pups per litter at birth (Mean ± S.D.)	0.36 ± 1.16	0.08 ± 0.27	0.29 ± 0.60	0.59 ± 1.12
Mean number of in-utero deaths per litter, including dead pups at birth (Mean ± S.D.)	0.86 ± 1.41	1.12 ± 0.99	0.82 ± 0.86	1.37 ± 1.31*
Post-implantation loss per group	0.033	0.071*	0.035	0.052
Post-implantation loss per litter (Mean ± S.D.)	0.091 ± 0.059	0.071 ± 0.059**	0.035 ± 0.047	0.051 ± 0.045*

*, **: statistically significant with p≤0.05 or p≤0.01, respectively

Results, F_1 Pups

Survival Indices: The data as originally presented and statistically analyzed in Table 9 for survival indices is predominantly based on total numbers viable and surviving pups/group. The sponsor was asked to reorganize Table 9 and to have the data and statistics based on pups/litter in each group. Both the original and revised tables are shown below. Based on the revised table, there appears to be a 5-fold increase in pups/litter that died between PPD 4 and PPD 21 compared to control (4.7% decrease in lactation index in the original table), but the differences were not statistically significant.

Table 9 - F_1 pups survival indices

UK-116,044-04 STUDY FOR EFFECTS ON PRE- AND POST-NATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION, IN SPRAGUE-DAWLEY RATS BY THE ORAL ROUTE

Study No. 56016

	CONTROL		5 mg/kg		15 mg/kg		50 mg/kg	
SURVIVAL INDICES								
24-HRS INDEX (%)	405/405	(100.0)	352/352	(100.0)	404/404	(100.0)	370/370	(100.0)
4-DAY INDEX (%)	397/405	(98.0)	348/352	(98.9)	400/404	(99.0)	364/370	(98.4)
LACTATION INDEX (%)	214/216	(99.1)	191/192	(99.5)	214/216	(99.1)	205/215	(95.3)

Supplementary data on F_1 pup survival indices

	Control	5 mg/kg	15 mg/kg	50 mg/kg
Number of viable pups at 24 hours (Mean ± S.D.)	14.5 ± 2.8	13.5 ± 2.4	14.4 ± 2.1	13.7 ± 2.1
Number of viable pups on day 4, before culling (Mean ± S.D.)	14.2 ± 2.7	13.4 ± 2.3	14.3 ± 2.1	13.5 ± 2.2
Number of remaining litters on day 4, after culling (8 pups per litter)	27/28	24/26	27/28	27/27
Number of viable pups on day 21 (Mean ± S.D.)	7.9 ± 0.3	8.0 ± 0.2	7.9 ± 0.3	7.6 ± 1.0
Number of pups which died between 24 hours and day 4, before culling (Mean ± S.D.)	0.29 ± 0.66	0.15 ± 0.37	0.14 ± 0.36	0.22 ± 0.42
Number of pups which died between day 4 (after culling) and day 21 (Mean ± S.D.)	0.07 ± 0.27	0.04 ± 0.20	0.07 ± 0.27	0.37 ± 0.88

Statistical analysis indicated no statistically significant changes

Mean Body Weight of F_1 Pups: Sponsor presented only the following summary table of mean body weight limited to control and high dose. Based on this table and individual animal data which also contained the means ± SD, there was a decrease in mean body weight of the F_1 offspring on PPD 1 in the high dose treated group compared to control (5.9% for males, 5.5% for females), which persisted to PPD 21, then into adulthood, up to PPD 77. There were no effects on mean body weight of F_1 offspring at mid and low doses.

Changes in mean body weight of high-dose F_1 pups

% change relative to control

Day p.p.	50 mg/kg	
	M	F
1	-6*	-5*
4	-7*	-6*
14	-10***	-9***
21	-9***	-8***
28	-5	-5
35	-7*	-5*
42	-6*	-4*
49	-7**	-4**
56	-4	-3
63	-4*	-4*
70	-4	-2
77	-5*	-3*

*, **, *** : statistically significant at p = 0.05, 0.01 and 0.001, respectively (sexes combined).

Table 19, in which Day 3 represents the weight of the adult F_1 rats at 3.5 months of age when they were mated, confirms that in males the decrease in body weight at high dose, compared to control, was still apparent and may have persisted for the life of the rats.

Table 19 - Mean body weight of F1 adults

UK-121,041-01 STUDY FOR EFFECTS ON PRE- AND POST-NATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION, IN SPRAGUE-DAWLEY RATS BY THE ORAL ROUTE

Study No. 96017

MEAN BODY WEIGHT (g) OF F1 MALES

DOSE		DAY 3	DAY 10	DAY 17	DAY 24	DAY 31	DAY 38	DAY 45	DAY 52
CONTROL	N	27	27	27	27	27	27	27	7
	MEAN	461 60	485 84	512.70	535.37	551.39	566.37	581.55	595 59
	S D.	50 51	46 55	51.16	53.52	56.91	62.84	63 96	52 91
5 MG/KG	N	24	24	24	24	24	24	24	7
	MEAN	458 05	479 03	499 35	524.14	545.23	556.15	568 35	595 17
	S D	45 81	45 63	50.64	50.48	52.56	59.83	62.28	76 18
15 MG/KG	N	27	27	27	27	27	27	27	7
	MEAN	460 22	481.27	507.49	532.27	550.69	561.77	579 90	567.57
	S.D.	35.20	38 86	39.12	44.40	45 67	53.26	55 20	40 44
50 MG/KG	N	27	27	27	27	27	27	27	6
	MEAN	439 74	458.11*	478 05*	500.08*	519 78	532.35	547 34	549 22
	S.D.	49 22	48 67	53 45	56.82	56.64	59.90	60.09	73 26

* statistically significant at p < 0 05

MEAN BODY WEIGHTS (g) OF F1 FEMALES

DOSE		DAY 3	DAY 10	DAY 17
CONTROL	N	27	11	1
	MEAN	258 65	271.49	296.50
	S.D.	19 15	23 73	
5 MG/KG	N	24	4	
	MEAN	263 94	261 43	
	S D	15 52	10 89	
15 MG/KG	N	27	11	
	MEAN	262 38	265.49	
	S D	19 77	13 80	
50 MG/KG	N	27	9	
	MEAN	256 92	273 02	
	S D	22 03	22 92	

Developmental Landmarks, Ophthalmology, Functional and Observational Battery, and Spontaneous Motor Activity:

There were no treatment-related effects on any of these parameters.

External and Visceral Findings of Pups Dead at Birth:

There were 4 runts, all in the same litter of a high dose treated dam; none in control or other treated groups.

External and Visceral Findings of Pups Dead During Lactation:

No compound related effects on total number of pups or litter incidence.

External and Visceral Findings of Pups Sacrificed on PPD 4:

No compound related effects on total number of pups or litter incidence.

External and Visceral Findings of Pups Sacrificed at Weaning:

No compound related effects on total number of pups or litter incidence.

Fertility and Reproduction Parameters: No effects.

Learning and Memory:

This study is considered to be deficient because of a failure to include learning and memory tests for the F_1 rats. Results of such a study, limited to these parameters in F_1 rats, will be submitted separately, Phase IV.

Results, F_2 Pups (Study No. 96017)

There were no effects on total number of live or dead pups at birth, nor on survival indices at 24 hours or 4 days.

Genetic Toxicology

All genetic toxicology tests were conducted in 1992 by Pfizer (Groton, CT).

I. Ames Test (92-912-01) GLP, QA

Batch: 2439/35

Strains: TA98, TA100, TA1535, TA1537, WP2uvrA and WP2pKM101

Concentrations: 0.01, 0.05, 0.2, 1.0, 5.0 mg/plate

Results: TA98 revertants were increased at 5 mg/plate under -S9 conditions. 3.2-fold in a "preliminary" test, 3.4-fold in the first "definitive" test and 2.1-fold in the second "definitive" test. In the latter test, no individual plate was ≥ 2-fold greater than the highest negative control plate, whereas in the first two tests each triplicate was 2.0 - 2.8-fold greater than the highest negative control plate It is noted that the positive control, 2-nitrofluorene, produced at least 13.5-fold more revertants than eletriptan, and the sponsor points out that for the first two experiments the TA98 negative control means were ~2 standard deviations below the historical control mean. Given the marginal response of strain TA98 at 5 mg/plate, additional concentrations between 1 and 5 mg/plate should have been tested.

Eletriptan was cytotoxic at 5 mg/plate for the TA100 (-S9 only) and WP2pKM101 strains, as indicated by a decreased number of revertants.

Query: According to OECD guidelines, 2-aminoanthracene (2-anthramine) should not be the sole positive control under +S9 conditions. It should be inquired of the sponsor whether the batches of S9 used (nos. 20871-46, 47, and 51) were qualified with another chemical.

II. Ames Test (92-912-01) GLP, QA

Batch: R1

Strains: TA98, TA100, TA1535, TA1537, WP2uvrA and WP2pKM101

Concentrations: 0.01, 0.05, 0.2, 1.0, 5.0 mg/plate

Results: Results were negative for all strains in two experiments, under both - and +S9 conditions. Eletriptan was cytotoxic at 5 mg/plate under -S9 conditions for strains TA100 and TA 1537, and under +S9 conditions for both *E. coli* strains, as indicated by a decreased number of revertants. For strain TA100, none of the 5 mg/plate triplicates were counted due to excessive cytotoxicity, indicating that additional concentrations between 1 and 5 mg/plate should have been tested.

Query — According to OECD guidelines, 2-aminoanthracene (2-anthramine) should not be the sole positive control under +S9 conditions. It should be inquired of the sponsor whether the batches of S9 used (nos. 20871-61, 64, and 65) were qualified with another chemical.

III. HGPRT Mutation Test in CHO Cells (92-912-01) GLP, QA

Batch — R1

Concentrations — -S9: 106, 127, 153, 183, 220, 264 µg/ml
+S9: 776, 854, 939, 1033, 1136, 1250 µg/ml

Results — Results were negative under both - and +S9 conditions. Cells were treated for 5 hrs, within the 3 - 6 hr time frame recommended by OECD. Cytotoxicity reached 76% at 264 µg/ml under -S9 conditions, acceptably close to the 80 - 90% stipulated by OECD. Cytotoxicity at 1250 µg/ml under +S9 conditions exceeded 90%, but at 1136 µg/ml was only 33%. Although it is generally required to have a concentration that produces 80 - 90% cytotoxicity, the steepness of the cytotoxicity response precluded such in this experiment.

IV. Chromosomal Aberration Test in Human Lymphocytes (92-912-01) GLP, QA

Batch — R1

Concentrations			
-S9:	test 1: 10, 20, 25, 30 µg/ml	(treated for 24 hr)
	test 2: 40, 50, 60 µg/ml	(treated for 24 and 30.5 hr)
+S9:	test 1: 10, 20, 40 µg/ml	(treated for 3 hr + 21 hr untreated)
	test 2: 10, 20, 30 µg/ml	(treated for 3 hr + 21 hr untreated)

Results — Under -S9 conditions, the three highest concentrations analyzed in the first test reduced the mitotic index (MI) by 40 - 44% (OECD recommends ≥ 50%), and at 40 µg/ml there was an insufficient number of mitotic cells for evaluation. In the second test, at the highest concentration of 60 µg/ml the MI was reduced by 43% at 24 hr and by 57% at 30.5 hr. In the first test the percent of abnormal cells was increased in treated cultures, but the increases were not statistically significant or dose-related, and no treatment exceeded the historical control range of 0 – 8%. Aberrations were not increased in the second test at either 24 or 30.5 hr.

Under +S9 conditions, 40 µg/ml in the first test reduced the MI by 47% (calculated using the sample that contained the requisite number of 100 cells, results from the second sample which contained only 44 cells were discounted because they may not be representative). In the second test, the MI was reduced by 45% at 30 µg/ml. The percent of abnormal cells was statistically significantly increased at the two highest concentrations in the first test, but no increase was seen in the second test. Comparing the results of the two tests, it appears that the increase observed in the first test may have been a consequence

of a particularly low negative control value because the negative control value in the second test equals or exceeds all values in the first test.
Results for –S9 and +S9 tests are summarized below

Eletriptan Concentration (µg/ml)	Abnormal Cells (%) -S9 test 1	-S9 test 2 24 hr	-S9 test 2 30.5 hr	+S9 test 1	+S9 test 2
0	2.5	3.0	2.0	0.5	4.0
10	6.5			2.0	2.5
20	6.5			3.5*	3.5
25	3.0				
30	6.0				1.5
40		3.5	4.5	4.0*	
50		2.5	2.5		
60		1.5	1.0		
Mitomycin-C	18.0	35.0	49.0		
Cyclophosphamide				17.0	22.0

*statistically significant, $p < 0.05$

Polyploidy was increased in all treated cultures in the second -S9 test, both at 24 (5.0, 5.0, 4.5% v. 1%) and 30.5 hr (6.5, 6.5, 8% v. 0%), but an increase was not observed in the first test (0, 0.5, 0, 0.5% v. 0.5%). When 1000 cells/culture were assessed at 24 hr, the percent of polyploid cells was determined to be 0.2, 1.4, 2.2, and 3.0 for control, 40, 50, and 60 µg/ml treatments, respectively.

V. *In Vivo* Micronucleus Assay, i.v. - CD-1 mice (92-912-01) GLP, QA

Batch — R1

Doses — 2.5, 5.0, 10 mg/kg i.v. for 3 days; 5/s/gr (smears prepared at 24 hr)

Results — HD animals were jittery, ataxic, and hypoactive. The sponsor states that based on an acute toxicology study, 10 mg/kg is the acute i.v. MTD. There was no effect of treatment on either the percentage of micronucleated PCE or the PCE/NCE ratio. It is noted that 1000 PCE/animal were evaluated rather than the 2000 stipulated by OECD.

VI. *In Vivo* **Micronucleus Assay, oral - CD-1 mice** (92-912-01) GLP, QA

Batch R1

Doses 75, 150, 300 mg/kg p.o. gavage for 3 days; 5/s/gr (smears prepared at 24 hr)

Results 1 HD M, 1 HD F, and 1 LD M died (it is not stated whether deaths were related to treatment). There were no clinical signs, but it has been shown that 1000 mg/kg p.o. is an acute lethal dose. There was no effect of treatment on the percentage of micronucleated PCE. There was a statistically significant decrease in the %PCE in HD M and F, indicating bone marrow toxicity; values were 34.8% in HD M v. 47.2% in control M and 45.0% in HD F v. 55.4% in control F. It is noted that 1000 PCE/animal were evaluated rather than the 2000 stipulated by OECD.

The following two tests were performed with the impurity identified as [redacted] structure shown below. Although it is not acknowledged by the sponsor, this impurity contains a Michael-reactive acceptor, which is a structural alert for mutagenicity. Upon contacting the sponsor on June 11, 1999, the sponsor indicated that they had recently performed two genotoxicity tests with this impurity. They submitted these studies on June 15, 1999, and they are reviewed below. Both studies were performed in 1999 by Pfizer (Groton, CT).

[redacted]

VII. **HGPRT Mutation Test in CHO Cells, Test of** [redacted] (99-1871-02) draft report

Batch 80300007A

Concentrations -S9: 20, 40, 50, 60, 70, 80, 90 mg/ml
+S9: 50, 75, 100, 125, 150, 175 mg/ml

Results Cells were treated for 5 hrs, within the 3 – 6 hr time frame recommended by OECD. Two tests under – and +S9 conditions were performed, but only the latter set of tests could be used to evaluate the genotoxicity of [redacted] because the negative controls in the first tests were notably in excess of historical controls (no explanation was offered). Results from the second set of tests are summarized below. The maximum concentrations tested resulted in sufficient cytotoxicity as well as precipitation. Results are clearly negative under –S9 conditions. Under +S9 conditions, increases in mutation frequency (MF) were observed at 125 and 150 mg/ml, but the increases were not dose-

related, the values are within the historical control range and the negative control is less than the 5.0 historical control mean. A statistical evaluation was not performed because the sponsor statistically evaluates only those studies in which one of the concentrations produces a MF of ≥ 20, which is one of the sponsor's criteria for a positive response.

Concentration (µg/ml)	-S9 MF (%)	-S9 D2 Survival (%)	+S9 MF (%)	+S9 D2 Survival (%)
	14.0	*100*	2.0	*100*
	11.5	*96*		
	7.0	*73*		
	16.5	*64*	0.5	*69*
	12.0	*43*		
	16.0	*34*		
			2.0	*60*
	5.5	*26*		
	4.0	*17*		
			2.0	*71*
			8.0	*38*
			4.5	*39*
			0.0	*7*
Ethylmethanesulfonate	269.5	*NT*		
3-Methylcholanthrene			73.5	*NT*

[a]Precipitation was noted at these concentrations

VIII. Chromosomal Aberration Test in Human Lymphocytes, Test of [redacted]

(99-1871-01) draft report

Batch 80300007A

Concentrations

-S9:	test 1: 15.8, 19.7, 24.6 mg/ml	(treated for 3 hr + 21 hr untreated)
	test 2: 15.4, 19.2, 30.0 mg/ml	(treated for 3 hr + 21 hr untreated)
	test 3: 30.0, 40.0 mg/ml	(treated for 3 hr + 45 hr untreated)
	test 4: 7.0, 10.1, 13.0 mg/ml	(treated for 24 hr)
+S9:	test 1: 13.1, 16.4, 25.6 mg/ml	(treated for 3 hr + 21 hr untreated)
	test 2: 7.7, 15.4, 19.2 mg/ml	(treated for 3 hr + 21 hr untreated)
	test 3: 7.7, 19.2 mg/ml	(treated for 3 hr + 45 hr untreated)

Results The maximum concentration evaluated in each test reduced the mitotic index by 48 – 62%, in accord with OECD guidelines. Results were clearly negative under –S9 conditions. Under +S9 conditions, there were small increases in the percent of abnormal cells; however, the increases were not statistically

significant and no replicate exceeded the historical control range of 0 – 4%. Results are summarized below.

Concentration (µg/ml)	Abnormal Cells (%) -S9 test 1	test 2	test 3	test 4	+S9 test 1	test 2	test 3
	0.5	2.5	2.5	2.0	0.5	0.5	0.5
				1.5			
						1.5	2.0
				0.5			
				1.5			
					0.5		
		1.0				1.0	
	0.0						
					1.0		
		1.5				3.0	2.5
	0.5						
	0.0						
					1.5		
		1.0	1.0				
			1.5				
Mitomycin-C	24.0	32.0	NT	15.0			
Cyclophosphamide					31.0	36.0	NT

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Carcinogenicity

I. Rat, 2 year dietary mix (94-912-03) GLP, QA
Pfizer Central Research (Groton, CT), conducted in 1994 – 1996

Sprague-Dawley rats – 3, 15, 75 mg/kg (lowered to 50 mg/kg for F after 8 months)
65/s/gr with 2 control groups (batch R109 and R203)

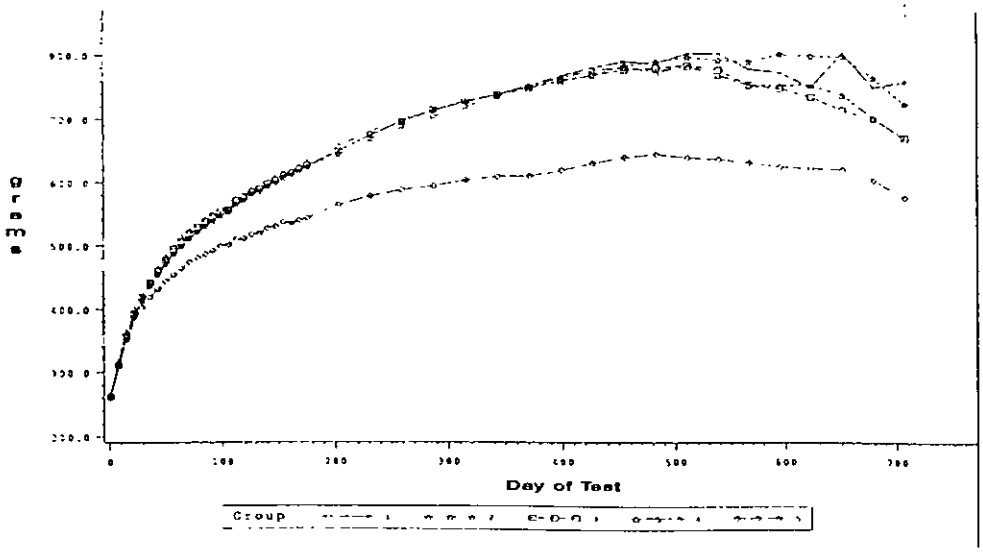
Mortality — There was no detrimental effect of treatment on survival throughout the study. In fact, survival in HD M exceeded that of controls from approximately 17 months onward. Survival at the end of the study is tabulated below.

Sex	Number of Animals Alive at Study Termination				
	C1	C2	LD	MD	HD
Male	17	22	23	19	42
Female	25	20	20	22	27

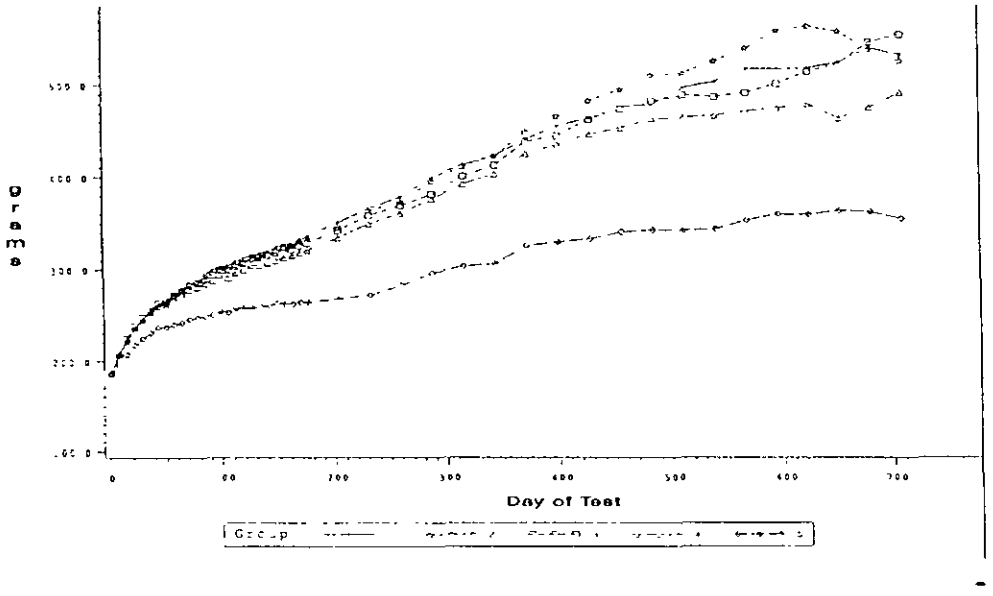
Clinical Signs — There were no notable clinical signs.

Body Weight — BW gain was reduced throughout the study in HD M and F such that BW's at the end of the study were 20 and 33% less than control, respectively (sponsor-supplied BW curves are provided below). Because of the excessive decrease in BW gain, the sponsor decreased the HD for F from 75 to 50 mg/kg after 8 months of treatment. From 17 months onward BW in MD F was 6 – 12% less than control, with differences being occasionally statistically significant. Effects on BW were generally paralleled by decreased food consumption, although the decreased BW gain in HD F was evident within the first weeks of the study, preceding the effect on food consumption. The decrease in food consumption does not appear to be related to palatability because it was not notable until weeks 6 – 8.

Males



Females



Hematology — Parameters were measured at 6, 12 and 18 months in 10/s/gr. There were no notable findings.

Clinical Chem — Parameters were measured at 6, 12 and 18 months in 10/s/gr. Bilirubin was increased 58 – 75% and 23 - 53% in all treated M and F groups, respectively, but only at 6 months. Triglycerides were decreased ~60% in HD F at 12 and 18 months. A similar decrease did not reach statistical significance in HD M at 18 months, but appears to be a drug-related effect based on individual animal data.

Toxicokinetics — Plasma concentrations of eletriptan were determined on Days 91 and 177 in 5/s/gr. Concentrations in the LD group were generally at or below the 4 ng/ml level of detection. Concentrations in the MD group were 41 and 49 ng/ml on Days 91 and 177, respectively, and in the HD group were 290 and 430 ng/ml, respectively.

Organ Weights — Absolute kidney weight was 20% less than control in HD M and absolute liver weight was 21% less than control in HD F. Relative brain and testis weights were 24 and 53% greater than control, respectively, in HD M. Relative heart, kidney and brain weights were 17, 25 and 40% greater than control, respectively, in HD F. The effect on organ weights likely reflects the decreased BW gain at the HD.

Pathology — The sponsor reports no treatment-related gross pathology (no data were provided). Notable histopathology changes are tabulated below and include an increased incidence of testicular interstitial cell adenoma in HD M. The sponsor states that the increased incidence was not significant after Bonferoni correction for multiplicity of testing, but Bonferoni correction in carcinogenicity studies is not accepted by the Agency because of it's tendency

to overcorrect given the sheer number of comparisons being made. The sponsor also attributes the increased incidence to the greater longevity of the HD M group (all testicular tumors were identified in animals surviving ≥ 19 months); however, the increase is statistically significant even after adjustment for survival. The 17.2% incidence exceeds the historical control range reported by [redacted] for studies conducted in 1984 – 1989 (1.4 – 10.0%, mean 4.7%). The incidence of histiocytic sarcomas was increased in MD M (6.2% v. 1.5%), but did not exceed the historical control range reported by [redacted] for studies conducted in 1984 – 1989 (1.4 – 7.1%, mean 1.6%).

Increased non-neoplastic histopathology was limited to HD M and included an increased incidence of liver eosinophilic foci, thyroid follicular cell hyperplasia, and pituitary *pars distalis* hyperplasia. The incidence of several histopathological findings were decreased in HD M and/or F, likely owing to the deficit in BW gain experienced at the HD.

	Incidence (63 – 65 tissues/gr examined)							
	Control[a]		LD		MD		HD	
	M	F	M	F	M	F	M	F
Neoplastic Findings								
Testes interstitial adenoma	4	na	1	na	3	na	**11**	na
Lymphoreticular System histiocytic sarcoma	1	0	0	0	4	1	2	1
Non-neoplastic Findings								
Liver, eosinophilic foci	8	9	6	7	5	5	25	8
periportal vacuolation	8	10	9	12	2	7	**1**	**1**
Thyroid, follicular cell hyperplasia	5	2	6	2	8	1	**15**	1
Pituitary, *pars distalis* hyperplasia	7	9	5	4	3	2	**14**	6
Adrenal, cortical vacuolation	15	5	20	4	14	3	**6**	4
Kidney, chronic nephropathy	49	24	53	14	52	20	37	**6**
Mammary Gland, fibroadenoma	0	19	0	11	0	15	0	**5**
Testes, periarteritis	14	na	19	na	15	na	**5**	na
tubular atrophy	16	na	21	na	15	na	**8**	na

[a]Of the two control groups the one that was the least different from the treated group was selected for inclusion in the table.

Summary

The incidence of testicular interstitial adenoma was increased in HD M (17.2% v. 6.2%). The sponsor attributed the increase to the greater longevity of HD M compared to control; however, the increase is statistically significant even after adjustment for survival. Furthermore, the 17.2% incidence exceeds the 1.4 – 10.0% historical control range reported by [redacted] for studies conducted in 1984 – 1989 (data closer to the time frame of this study are not available). The only other tumor incidence that was notably increased was that of histiocytic sarcomas in the lymphoreticular system of MD M (6.2% v. 1.5%). Although a similar increase did not occur at the HD, the excessive decrease in BW gain at the HD (BW 20% less than control at study termination) may have

decreased tumor expression at the HD. The 6.2% incidence of histiocytic sarcoma at the MD did not exceed the 1.4 – 7.1% historical control incidence reported by ———— for studies conducted in 1984 – 1989 (data closer to the time frame of this study are not available).

Non-neoplastic changes observed in HD M included increased incidences of eosinophilic foci in the liver, follicular cell hyperplasia in the thyroid and *pars distalis* hyperplasia in the pituitary. There were also a few changes indicative of improved general health in HD M and F, likely related to the decreased BW gain observed at the HD. The incidences of hepatic periportal vacuolation, adrenal cortical vacuolation, chronic nephropathy, testicular periarteritis, testicular tubular atrophy, and mammary gland fibroadenoma were decreased in HD M and/or F.

The excessive decrease in BW gain at the HD may have compromised tumor expression, making the 15 mg/kg MD the highest dose from which tumor data can be reliably evaluated. On a mg/m^2 basis this dose is approximately equal to the proposed maximum recommended daily dose of 2 x 80 mg. The plasma levels achieved at this dose were approximately 20% of the Cmax achieved in humans given an 80 mg dose. No AUC estimations were made in this study; however, extrapolating linearly from results in the dose range-finding study (100, 200, 300 mg/kg), the AUC achieved in M and F rats at 15 mg/kg is predicted to be approximately equal to the 3000 ng.h/ml exposure achieved in humans at the proposed maximum recommended daily dose. The AUC extrapolated for the 75/50 mg/kg dose is approximately 2 times the exposure achieved in humans at the proposed maximum recommended daily dose

It appears that higher doses could have been achieved by gavage rather than dietary administration. In a one month gavage study (97075) in which the HD was 100 mg/kg, there was no effect on BW and toxicity was limited to increased liver weight (~20%) and thyroid follicular hypertrophy in F only. Furthermore, essentially no toxicity was observed in a 6 month gavage study at the HD of 50 mg/kg. Extrapolating toxicokinetic data from the 6 month study, exposure for M and F rats at a 100 mg/kg gavage dose is predicted to be 3 and 6-fold, respectively, the AUC achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg.

II. Mouse, 2 year dietary mix (94021) GLP, QA

This study was reviewed by Barry Rosloff, Ph.D. The tables and figures referred to have not been attached.

A) DOSAGE

50/sex at 0, 0, 20, 90, or 400 mg/kg/day, in diet

Strain: CD-1

Drug batch numbers: R107 and R109

Lab performing study: Pfizer
Centre de Recherche
37401 Amboise Cedex
France

Dates of study: 1994-1996

B) RESULTS

1) Observed signs.

No drug effects.

2) Mortality

Results shown in attached figures.

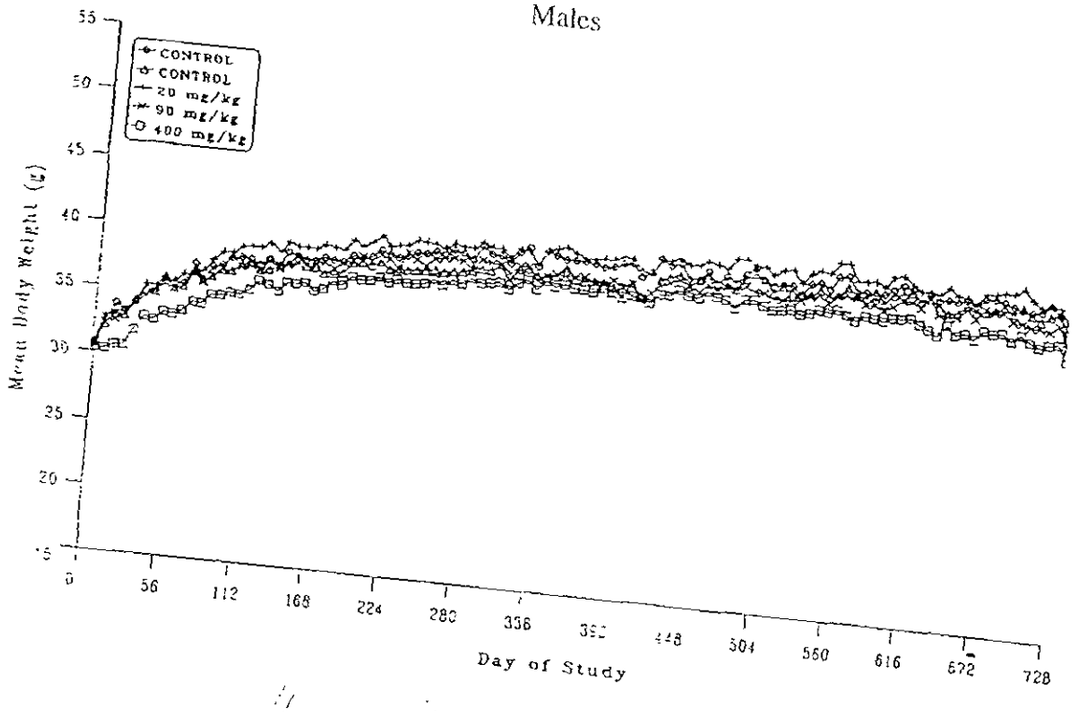
The sponsor concludes that mortality was decreased in MD and HD F. (Overall survival = 44%. 58% and 68% in control F, MD F, and HD F, resp.) However, as indicated in the attached figure, mortality in all M groups, although similar to controls at the end of the study, was less than that in controls during most of the 2nd year (not dose-related).

3) Bodyweight

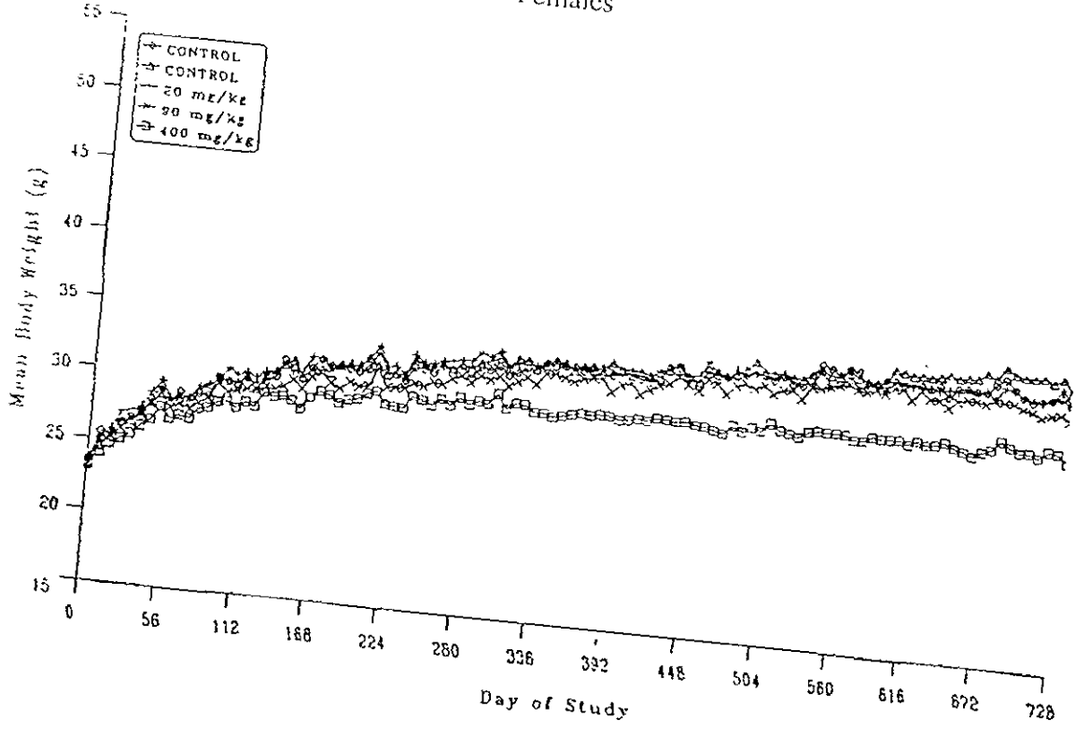
Weight gain was slightly decreased in HD M and HD F starting from the first week of treatment. Weights near the end of the study were approximately 5% and 13% below control in HD M and HD F, resp. Weight gain was slightly decreased in MD F beginning after the 2nd month of treatment, although this only occasionally reached statistical significance; weights near the end of the study were approximately 5% below control. Weight gain in LD M was very slightly increased after 3 months.

Sponsor-supplied bodyweight curves below.

Males



Females



4) Food Consumption

Slightly decreased at HD of both sexes throughout the study, with the notable exception that consumption was slightly (and statistically significantly) increased in HD F during week 1. As with weight gain, food consumption was slightly decreased in MD F, although this did not become apparent until later in the study (approx. 8 months) than did the decrease in weight gain. Food consumption was sporadically slightly increased in LD M.

Food consumption curves are attached.

5) Water Consumption

At HD, slight decreases throughout most of study (although slightly increased first week). Slight decreases in MD F during latter part of study.

6) Ophthalmoscopic exam

(Done in 25/sex in controls and HD pre-study; repeated every 6 months in survivors among these animals)

No drug effects.

7) Hematology

(Done at termination)

Slightly decreased RBC, Hb, and Hct, and slightly increased platelets, in HD M. Very slight, non-statistically significant changes in same directions as above seen in MD M.

Other parameters measured: RDW, large unstained cells, WBC, differential, bone marrow smears. (No summary data shown for the latter).

8) Blood chemistry

(Done at termination)

a) ALT, AST, and AP increased in HD M. Mean values approx. 2x control; highest individual value at HD approx. 2.3x, 3x, and 1.3x highest concurrent control for ALT, AST, and AP, respectively.

b) Glucose decreased in MD and HD M (D-R) and HD F; mean value at HD approximately 80% of control.

c) Na very slightly increased in HD M. (Mean value approximately 2 mmol/L above control).

d) Cl moderately increased at MD and greatly increased at HD, said to be due to interference with the assay by the bromide moiety of the drug.

e) Other parameters measured: K, Ca, urea, cholesterol, triglycerides, protein albumin

9) Urinalysis not performed

10) Organ weights

Absolute and relative liver weights increased in MD and HD M. Relative weights were approximately 1 13 and 1.5x control at MD and HD, resp. Relative liver weight was slightly increased in HD F (1.1x control) with no effect on absolute weight.

11) Gross pathology

Text states no effect; no summary table presented.

12) Histopathology

(Organs shown in the list below, plus organs with macroscopic abnormalities, were examined in all groups. Summary tables did not break down results by animals which survived to termination and those which did not. These tables are attached [separate tables for neoplastic and non-neoplastic findings].)

Adrenal glands
Aorta
Brain
Cervical lymph node
Colon
Duodenum
Epididymides
Eyes/Harderian glands
Gall bladder
Heart
Ileum
Kidneys
Liver
Lung
Mammary gland/skin
Mesenteric lymph node
Oesophagus
Ovaries
Pancreas
Parathyroid
Pituitary gland
Prostate
Salivary glands
Sciatic nerve
Spleen
Sternum with marrow
Stomach
Striated muscle
Testes
Thymus
Thyroid gland
Trachea
Urinary bladder
Uterus
Vagina

a) Liver

The following showed increased incidence in HD M: hepatocellular adenoma, foci of cellular alteration, single cell necrosis, pigmentation (mainly lipofuscin in Kupffer cells), and various "centrilobular changes" (hepatocyte hypertrophy, karyomegaly, heterogeneous cytoplasm). Centrilobular changes also seen in 2/50 MD M and 2/50 HD F. (Incidence values shown in sponsor's summary tables; some also shown in the excerpt below taken from the "Results" section which also contains additional descriptions of some the lesions). Note that eosinophilic, but not basophilic adenomas were increased; also note that according to the sponsor's descriptions some other drug-related findings were also eosinophilic in nature. The incidence of liver carcinomas was not increased.

Liver

Findings in the liver were generally limited to the high-dose males and consisted of an increased incidence of a spectrum of centrilobular findings, foci of cellular alteration and eosinophilic adenomas, all of which correlated with the increased organ weight.

The centrilobular microscopical findings usually occurred together and consisted of:

- Hepatocellular changes characterized by enlargement of hepatocytes which displayed variably enlarged nuclei (karyomegaly) and heterogeneous cytoplasm containing deep eosinophilic to amphophilic scattered small irregular aggregates within a light eosinophilic background. Hepatocellular changes were minimal (involving a few centrilobular hepatocytes) to severe (diffuse). The hepatocellular changes also occurred in 2/50 mid-dose males and 2/50 high-dose females.
- Single cell necrosis characterised by scattered necrotic hepatocytes.
- Pigmentation consisting mainly of lipofuscin within the cytoplasm of Kupffer cells.

Mixed foci of cellular alteration were recorded only in the high-dose male group. They were composed of enlarged hepatocytes with nuclear and cytoplasmic characteristics similar to those described above for the centrilobular hepatocellular changes. There was also a slight increase in the incidence of basophilic foci.

The incidence of hepatocellular adenomas was slightly increased owing to the presence, within the high-dose male group, of 7 adenomas of the eosinophilic type made up of enlarged eosinophilic hepatocytes. The incidence of both basophilic adenomas and hepatocellular carcinomas was similar to controls.

In addition, the incidence of spongiosis hepatis was slightly increased in the high-dose female group (5/50 vs 1/50 in control female groups). In the absence of any associated compound-induced hepatic changes, this variation was considered to be of no toxicological importance.

Relevant hepatic findings in males

	Controls 1 (n=50)	Controls 2 (n=50)	20 mg/kg (n=50)	90 mg/kg (n=50)	400 mg/kg (n=50)
Centrilobular findings:					
Centrilobular hepatic changes				2	22 ***
Single cell necrosis	7	5	7	8	24 ***
Pigmentation		2		3	21 ***
Foci of cellular alteration:					
Basophilic foci		2	1	2	5 **
Mixed foci					10 ***
Neoplasms:					
Adenoma *	2	7	2	3	12 **
Basophilic	2	7	2	3	5
Eosinophilic					7
Carcinoma	3	2	4	4	4

,* = statistically significant at p=0.01, p=0.001
* Adenoma was analyzed statistically as a whole only

b) Harderian gland

The incidence of adenoma was increased in HD M (12% vs 3%, 6% and 6% in controls, LD and MD, resp.). The incidence of hypersecretion in Harderian gland was also increased in HD M (70 % vs 42 % in control). The incidence of hyperplasia was not increased.

Although apparently not considered drug-related by the sponsor, the incidence of harderian gland adenoma in females was 0%, 6%, 4% and 6% in controls, LD, MD, and HD, resp. The incidences of hypersecretion and hyperplasia were not increased in females.

C) SUMMARY

A 2 year dietary carcinogenicity study was performed in CD-1 mice at daily doses of 20, 90, and 400 mg/kg. There were no drug-related signs or effects on opthalmoscopic exams. Mortality was decreased in MD and HD F. Although there was no drug effect on percent survival in males at termination, mortality was lower than controls in all male groups (not D-R) during the second year of the study. Bodyweight gain and food consumption were decreased in MD and HD F and HD M; final weights were 5%, 13%, and 5% below controls, respectively. Hematology and blood chemistry exams showed (1) slightly decreased RBC, Hb, and Hct. and slightly increased platelets, in HD M and equivocally in MD M, (2) increased ALT, AST and AP in HD M, (3) decreased glucose in MD and HD M and HD F, and (4) increased chloride at MD and HD said to be due to assay interference by the drug.

Absolute and relative liver weights were increased in MD and HD M; relative (but not absolute) liver weight was slightly increased in HD F. Gross pathology exams were said to show no drug effect although no summary tables were presented. Histopathology exams showed an increase in eosinophilic hepatocellular adenomas in HD M (14% vs 0% in controls; incidence of total [eosinophilic + basophilic] adenomas = 24% vs 9% in controls). Also increased in liver of HD M were foci of cellular alteration, single cell necrosis, pigmentation of Kupffer cells, and centrilobular changes (hepatocyte hypertrophy, karyomegaly, heterogeneous cytoplasm). (Centrilobular changes also seen in 2/50 MD M and 2/50 HD F.) There were no drug effects on the incidence of hepatocellular carcinoma.

There was a slight increase in the incidence of harderian gland adenoma in HD M (12% vs 3% in controls). The incidence of hypersecretion in harderian gland was also increased in HD M; the incidence of hyperplasia was not. Although apparently not statistically significant by the sponsor's analysis, it is noted that the incidence of harderian gland adenomas in females was 0%, 6%, 4%, and 6% in controls, LD, MD and HD, respectively. The incidence of hypersecretion and hyperplasia were not increased in females.

D) EVALUATION

Although the drug did not cause any observed signs, an MTD may be considered to have been reached based on decreased weight gain; final weights at the HD (400 mg/kg) were 5% and 13% below controls in M and F, respectively. (Slight decreases in weight gain were also seen at this dose in a 3 month range-finding study; higher doses were not tested). Since food consumption was decreased in the same groups in which weight gain was decreased, the

possibility of poor palatability as an explanation arises. In HD M, both food consumption and bodyweights were decreased from the first week of treatment, which would support this explanation. However, in HD F, although bodyweights were decreased from the first week, food consumption showed a slight increase during the first week. Furthermore, in MD F, decreases in weight gain did not become apparent until after the second month, and decreased food consumption did not become apparent until 8 months. It thus appears likely that poor palatability is not a necessary cause of the decreased weight gain, although a role for this cannot be ruled out (especially in HD M).

Regarding the adequacy of the doses used, the sponsor also states that the AUC for parent drug at a dose of 400 mg/kg (22 ug.hr/ml, obtained in the 3 month range-finding study, results attached) is about 33-fold higher than that produced in humans "at the maximal daily clinical dose". However, note that using a maximum human dose of 80 mg b.i.d., and an estimated daily AUC of 3 ug.hr/ml (per information provided by Biopharm reviewer), a factor of 7 is calculated. It is also noted that no comparative exposure data for metabolites were presented for this highly metabolized drug.

Although hepatocellular adenoma is a common tumor type in this strain of mice, the increased incidence in HD M was clearly drug-related, particularly in view of the increase in foci of cellular alteration. The sponsor suggests that the increase in adenomas is related to hepatic enzyme induction; however, it is noted that the enzyme-inducing effect (elevated liver P-450 content) as measured in the 3 month range-finding study was thought to be small. (Also note that aside from a neoplastic effect, other liver toxicity was demonstrated in this study, including elevations of ALT, AST and AP, increased liver weight, and various histopathological changes.)

The small increases in harderian gland adenomas are somewhat equivocal. Although statistically significant by the sponsor's analysis, the report states that a drug effect in HD M is "unlikely" since the incidence (12%) was said to be "only slightly above our historical data;" however, the only such data cited was an incidence of 5/50 in a control group "of a recent study". (In contrast, it is stated in a 1990 book [Faccini, et. al., Mouse Histopathology], that the historical incidence at Pfizer/Amboise [where the present study was performed] is under 2%. On the other hand, other published data do show higher values for CD-1 mice, e.g. 13% [range 0-18%] in males and 5% [range 0-7%] in females in a recent Charles River publication). There was no strong evidence for an earlier onset of adenomas in HD M; 3 were found at termination and 1 each on days 684, 709, and 734; all 3 control tumors were found at termination. The fact that survival was greater than controls in most drug groups may have played a role in the increased tumor incidence, although the sponsor's analysis, which presumably took this into account, still showed a statistically significant increase in HD M (when both control groups were combined). In support of an effect in HD M was the finding of increased hypersecretion in this group. Increased hypersecretion was not seen in females. Increased hyperplasia was not seen in males or females.

SUMMARY AND EVALUATION

Pharmacology

The therapeutic action of triptans is generally attributed to two mechanisms, direct vasoconstriction of cerebral vasculature, mediated primarily by 5HT1B receptors, and blockade of trigeminal nerve-stimulated dural inflammation, mediated by 5HT1D and possibly 5HT1F receptors. Eletriptan has been demonstrated to have nanomolar affinity for 5HT1B, 1D and 1F receptors, and to act as an agonist at the 1B and 1D subtypes (activity at 1F receptors was not investigated).

A sponsor-supplied summary of the pharmacology studies conducted with eletriptan has been attached in Appendix A. Because of the impact on labeling and marketing, data comparing the vasoconstrictive effects of eletriptan and sumatriptan on coronary and cerebral arteries were reviewed in detail. The sponsor contends that *in vitro* and *in vivo* data indicate that eletriptan is more selective than sumatriptan for vasoconstriction of cerebral versus coronary arteries. Examination of the data indicates that the differences seen *in vitro* are not biologically significant; however, the *in vivo* data do indicate that eletriptan is slightly more selective than sumatriptan for reducing carotid blood flow versus reducing coronary artery diameter. The clinical relevance of this finding is unknown, particularly given that the maximal vasoconstriction (carotid and coronary) is similar for both drugs.

Absorption, Distribution, Metabolism and Excretion (ADME)

Absorption of eletriptan appears to be extensive across species (mice, rats, rabbits, dogs) because the majority of an oral dose is excreted as metabolites (this statement presumes that gastrointestinal metabolism is limited). Bioavailability was estimated to be 50 – 60% in dogs and mice, but only 13% in rats, which suggests an extensive first pass effect or nonlinear pharmacokinetics in rats (bioavailability was estimated from a single oral dose). Absorption was fairly rapid, with Tmax being ≤ 1 hr across species. Exposure increased with dose in rat and dog toxicology studies. In rats, exposure was approximately two-fold greater in F than M. Elimination half-life was determined to be 2 hr in rats given a 10 mg/kg dose and 5 hr in dogs given a 1 mg/kg dose. However, kinetic data collected in toxicology studies indicate that the half-life in dogs is inversely related to dose; this relationship between half-life and dose did not occur in rats.

Distribution of drug-related material was not studied after oral dosing. When a radiolabeled 3 mg/kg dose was given intravenously to rats, distribution was rapid, with the concentration of radioactivity in the brain at 0.1 hr reaching 25% of the blood concentration and concentrations in other tissues exceeding the blood concentration. By 24 hrs after dosing, concentrations were generally < 2% of the 0.1 hr values except for the retina and tissues involved in excretion. The retainment of radioactivity in the retina suggests the binding of eletriptan and/or metabolites to melanin; however, binding to pigmented skin was notably less, with barely detectable amounts of radioactivity present by 24 hr. *In vitro* protein binding was consistent over the concentration range of 0.01 – 1 µg/ml, and averaged 62, 61, 76, 52, and 76% for mouse, rat, rabbit, dog and human plasma, respectively. The 1 µg/ml concentration is five times the Cmax associated with an 80 mg dose in humans.

Eletriptan was extensively metabolized by rats, mice, rabbits, dogs and humans. One hour after a single oral radiolabeled dose was given to mice, rats, rabbits, dogs and humans, eletriptan accounted for less than half of the circulating radioactivity, except in male rats. Furthermore, parent drug accounted for less than one third of radioactivity in excreta. Six principal metabolic pathways were identified in animals, pyrrolidine N-demethylation, pyrrolidine N-oxidation, tetracyclic quaternary ammonium formation, di-oxidation, aliphatic hydroxylation β– to the phenyl sulphone group and carbonyl formation mainly on the pyrrolidine ring. The first four pathways were also identified in humans. The N-desmethyl metabolite was shown to exhibit vasoconstrictive properties similar to those of eletriptan, but is not present in large enough amounts to contribute substantially to the clinical effect.

Excretion of drug-related material was nearly complete within 48 hr in all species tested (72 hr for human feces). In animals the majority of drug-related material was excreted in the feces with the balance being excreted in the urine, whereas in humans excretion was equally divided between urine and feces. Biliary excretion appears to be extensive as 53% of the dose was recovered in the bile of cannulated rats within 2 hr of a 1 mg/kg i.v. dose, and the metabolite profile in excreta was similar after oral and intravenous dosing.

General Toxicity

Three chronic toxicology studies were performed with eletriptan, a 6 month study in rats and 6 and 12 month studies in dogs. In all of the studies toxicity was minimal even at the HD, indicating that doses should have been higher, particularly since toxicokinetic coverage relative to clinical exposure was minimal or nonexistent. In the rat study (5, 15, 50 mg/kg) there were no clinical signs. The slight BW increase that occurred in MD and HD F may have been related to increased water consumption (observed in HD F), which may also have been responsible for the observed increase urine volume. Clinical pathology changes were minimal. Leukocytosis occurred in a few HD M, but may be accounted for skin abscesses, and monocytes were increased in a few HD F. Cholesterol was modestly increased in MD and HD M and F, and triglycerides were moderately increased in MD and HD F. There was a minor increase in relative liver weight in HD F and a minor decrease in relative testicular weight at all doses. Histopathology findings included hemosiderosis in the spleen of 4/20 HD F and an increased incidence of progressive chronic nephropathy in HD M (18/20 v. 12/20) and F (9/20 v. 2/20). Because nephropathy in male rats is common, it is difficult to determine whether the incidences observed in this study reflect a treatment effect. The incidences of thrombosis in the heart and cysts in the glandular mucosa of the stomach increased in HD F, but both incidences were still less than the corresponding incidences in control M. The AUC's obtained in HD M and F were only 1.4 and 2.8 times, respectively, the 3000 ng.h/ml exposure achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr). The AUC's in rats were extrapolated from 1 hr rather than 0 hr, but based on the graphic representation of the data this would not be expected to significantly affect the AUC calculation. The Cmax's obtained in HD M and F were 3.6 and 5.7 times, respectively, the 200 ng/ml Cmax achieved in humans given an 80 mg dose.

The main finding throughout both the 6 month (1.25, 2.5, 5 mg/kg) and 12 month (0.6, 1.25, 4 mg/kg) dog studies was an increase in HR after dosing. In the 12 month study, increases were seen only at the HD of 4 mg/kg (mean increase 33%, individual increases up to 72%), whereas increases were dose-related and seen at all doses in the 6 month study. In the 6 month study the increases in HR were accompanied by 23 and 32% increases in systolic arterial BP at

the MD and HD, respectively; this effect was not reproduced in the 12 month study, but had been seen at similar doses in range-finding studies. ECG's indicated that in addition to the QT interval being shortened, likely as a result of the increased HR, P wave duration and amplitude were increased. Clinical signs were limited to mydriasis (all groups except the LD group in the 12 month study) that resolved prior to subsequent dosing. The transient corneal spots reported at the HD during the first week of the 1 month study (1.25, 2.5, 5 mg/kg) were not noted in the 6 or 12 month study, perhaps simply because ophthalmology exams were not performed until 5 – 6 months. There was no consistent clinical pathology between the two studies. One HD M in the 12 month study was slightly anemic throughout the study and experienced a large decrease in PLT that only partially recovered during the course of the study. The decrease in platelets likely contributed to the increase in prothrombin time for this animal. Whereas in rats triglycerides were increased in females, they were increased in males at the MD and HD in the 6 month dog study, but a similar effect was not seen in the 12 month study. As in the chronic rat study, the dog studies did not clearly identify target organs. The cardiac fibrosis observed in 2/3 M given 5 mg/kg in the 1 month study and in 1/2 F given 7.5 mg/kg in the 2 week study did not occur in the chronic studies. Likewise, the perivascular cuffing which was observed in the brains of 2/8 HD dogs in the 6 month study appears not to be treatment-related because in the 12 month study it was observed in 1/8 LD and 2/8 MD dogs, but no HD dogs. The AUC's achieved at the HD in both the 6 and 12 month studies were less than the 3000 ng.h/ml $AUC_{0-\infty}$ achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg (doses separated by > 2hr). The AUC comparison is made with the caveat that the dog AUC was calculated for 1 – 7 hr only; however, the graphic presentation of the data indicates that this time frame appears to account for more than half of the total exposure. The Cmax's obtained at the HD in the 6 and 12 month studies were 2.1 and 1.4 times, respectively, the 200 ng/ml Cmax achieved in humans given an 80 mg dose.

The doses selected for the chronic rat and dog studies did not approximate MTD's or provide sufficient toxicokinetic coverage. It is difficult to determine exactly how much greater the doses could have been. For the rat, based on the results of a one month study (no. 97075) it appears that the HD could have at least been doubled to 100 mg/kg. Even when this dose was used as the HD in the one month study, toxicity was limited to a ~20% increase in liver weight and thyroid follicular hypertrophy in F only. Based on range-finding studies it is unclear what the MTD is in rats, although it is clear that 1000 mg/kg is lethal. On days 2 – 3 of a 5 day study, death occurred in 2/4 animals within 15 minutes of being given the HD of 400 mg/kg; both animals were found to have full stomachs and one was also found to have liquid (presumably test material) in the lower airway. The sponsor attributed the deaths to drug-induced inhibition of gastric motility that resulted in inhalation of rejected test solution; however, the presence of test material in the lung could also be indicative of a gavage error. On days 3 and 7 of a 14 day study in rats, 2/5 F (0/5 M) given 200 mg/kg died, but there was no obvious cause of death. Unlike the deaths that occurred at 400 mg/kg in the 5 day study, the deaths at 200 mg/kg were delayed ≥ 2.5 hr after dosing. In both of the range-finding studies, the incidences of dyspnea and decreased activity were such that animals other than those that died were affected, lending some support to the possibility that the deaths were treatment-related.

For dogs, the 4 mg/kg HD used in the 12 month study may have been within 3-fold of the MTD, based on results from a dose range-finding study. In the range finding study, 1 M and 1 F dog were given doses of 6, 12.5, 6, 6, and 9 mg/kg on successive days. Both dogs experienced transient incoordination of hindlimbs after the 12.5 mg/kg dose, and the F was also affected after the 9 mg/kg dose. Because of the design of the study, it is not possible to determine if tolerance

to this effect would have developed over time. Other changes observed were similar to those seen in the chronic dog studies and included increases in HR and systolic arterial BP.

Developmental and Reproductive Toxicity

Developmental and reproductive toxicity studies were conducted in rats and rabbits. In the rat fertility study (5, 15, 50 mg/kg), mating and fertility were unaffected by treatment. There were no effects on reproductive parameters, nor were there signs of general toxicity beyond transient salivation. As such, the doses should have been greater, particularly in light of the fact that exposure estimates for the HD are only 1.4 – 2.8 times that achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg. The sponsor cites the decreased BW gain observed at 100 mg/kg in the rat embryofetal development study (see below) and the thyroid follicular hypertrophy observed at 100 mg/kg in a 1 month general toxicity study (no. 97075) as justification for the doses selected. However, the latter effect does not define an MTD and the BW gain deficit observed in the embryofetal development study is likely specific to the pregnancy status of the females during dosing, as it did not occur in the 1 month general toxicology study.

Eletriptan was not teratogenic in the rat embryofetal development study (10, 30, 100 mg/kg). Fetal weight was decreased 6 and 4% in HD M and F fetuses, respectively (the decrease in F fetal weight was not statistically significant). The number of HD fetuses (litters) with minor vertebral alterations was 11 (8) versus 3 (3) in controls, and the number exhibiting minor sternebral alterations was 4 (3) versus 1 (1) in controls. The percentages of fetuses displaying delayed ossification of vertebra and metacarpi doubled at the HD, but was similar to or less than historical control means. There was delayed ossification of the skull in a few HD fetuses, but the percentage was similar to historical control values. Doses selected for this study were adequate as evidenced by the 14 and 26% deficits in dam BW gain during the treatment period at the MD and HD, respectively. The decreased BW gain resulted in GD20 BW's that were 4 and 6% less than control at the MD and HD, respectively. The $AUC_{0\text{-}7hr}$'s achieved at the MD and HD were approximately equal to and 2.4 times, respectively, the 3000 ng.h/ml $AUC_{0\text{-}\infty}$ achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg. These comparisons underestimate the rat/human AUC ratios because the rat AUC was calculated for 0 – 7 hr only and the graphic presentation of the data indicates that significant exposure may occur after 7 hr (furthermore, 280 ng/ml was still detected in the HD group prior to dosing).

In the rabbit embryofetal development study (5, 10, 50 mg/kg), fetal weight was decreased 7% at the HD. The sponsor also reports a decreased maternal BW gain at the HD, but the effect was minimal (adjusted BW as of GD15 was 2% less than control) and not likely biologically relevent. The incidence of vena cava deviation was increased in all treated groups (3/132 [2/19] C, 8/138 [8/19] LD, 5/139 [4/19] MD, and 7/135 [5/17] HD fetuses [litters]), as was the incidence of fused sternebrae (0/132 [0/19] C, 8/138 [6/19] LD, 4/139 [3/19] MD, and 2/135 [2/17] HD fetuses [litters]). Vessel and sternebral alterations are the types of anomalies detected in developmental studies conducted with other triptan drugs. Gastroschisis was observed in 2/138 (1/19) LD, 1/139 (1/19) MD, and 1/135 (1/17) HD fetuses (litters), but does not appear to be a teratogenic effect because the affected HD fetus and one of the affected LD fetuses were severely underweight, which could have compromised normal development. Furthermore, the dam of the single affected HD fetus did not gain weight from GD6 – 15, so maternal toxicity may be responsible for the effect in that fetus. The only other major anomaly was scoliosis in 1 LD fetus. Although there were no treatment-related clinical signs, the doses

selected were adequate because in a dose range-finding study 100 mg/kg caused notable decrements in BW gain and the death of 3/7 pregnant rabbits. On a mg/m^2 basis, the 5, 10 and 50 mg/kg doses were less than, approximately equal to, and approximately 6 times, respectively, the proposed maximum recommended daily dose of 2 x 80 mg.

In the rat peri- and post-natal study (5, 15 and 50 mg/kg), the BW of HD F1 pups was decreased 5 – 10% during lactation, an effect that persisted into adulthood, albeit at a reduced percentage (BW's after postnatal day 49 were 2 - 5% less than control). There were no effects on developmental landmarks, spontaneous activity, functional battery observations, external and visceral findings, or reproductive function in F1 pups. Effects on learning and memory were not assessed: the sponsor has agreed to conduct such a study as a Phase IV commitment. The HD decreased F0 maternal weight gain between GD 6 – 9; thereafter the weight gain pattern followed that of controls, but the effect during GD 6 – 9 was such that most subsequent BW measurements throughout gestation and lactation were minimally (3 – 4%) less than control. Although there is mention of increased F0 post-implantation loss, examination of the individual litter data indicates that this results merely from an increase in the number of litters with 1 – 2 losses/litter (17 HD litters v. 9 control litters affected). A similar effect was also observed at the LD, but not at the MD, making a relationship to treatment tenuous. Similarly, a decrease (not statistically significant) in HD F1 pup survival occurred between days 4 and 21, but examination of individual litter data shows this decrease to be the result of losses of 1 – 2 pups in a few litters (6 HD litters v. 3 control litters affected). Relying on toxicokinetic data generated in nonpregnant rats, the AUC associated with the 50 mg/kg dose, which produced decrements in pup weight, was 3 times the 3000 ng.h/ml AUC achieved in humans at the maximum recommended daily dose of 2 x 80 mg. The AUC associated with the 15 mg/kg NOAEL was less than the AUC achieved in humans at the proposed maximum recommended daily dose.

Genotoxicity

Eletriptan was evaluated for genotoxicity in two Ames tests, an *in vitro* mammalian mutation test, an *in vitro* mammalian chromosomal aberration test and two *in vivo* micronucleus tests. Results were negative in the HGPRT mutation test in CHO cells and in the intravenous and oral mouse micronucleus tests. A positive response was seen under –S9 conditions with the TA98 strain in the first Ames experiment at the highest concentration of 5 mg/plate; however, this was not reproduced in the second Ames experiment, and may be attributed to the negative control means in the first experiment being two standard deviations below the historical control mean. Results were equivocal in the chromosomal aberration experiment in human lymphocytes. In the first trial, under –S9 conditions the percent of cells with aberrations exceeded control at all doses (6.5, 6.5, 3.0 and 6.0% v. 2.5%), but the increases were not statistically significant or dose-related. Under +S9 conditions, the percent of cells with aberrations was statistically significantly increased at the two highest concentrations tested (3.5 and 4.0% v. 0.5%; historical control reported as 0 – 3%, but 4% occurred in the second trial of this experiment). In the second trial, results were negative under both – and +S9 conditions.

During the course of the review of this NDA, it was noticed that the synthetic intermediate ——— contains a Michael-reactive center, which is a structural alert for mutagenicity. Negligible amounts (——————— were present in batches used for most of the carcinogenicity testing duration, yet the requested specification is ——. Upon contacting the sponsor on June 11, 1999, the sponsor informed us that they had recently completed an HGPRT mutation assay in CHO cells and a chromosomal aberration assay in

human lymphocytes with [redacted] Draft reports were submitted on June 15, 1999, and a review of the data indicates that [redacted] is not genotoxic.

Carcinogenicity

Two carcinogenicity studies were conducted, one in Sprague-Dawley rats and one in CD-1 mice. In the 2 year dietary study in rats (3, 15, 75 mg/kg, lowered to 50 mg/kg in F after 8 months because of reduced BW gain), the incidence of testicular interstitial adenoma was increased at the HD (11/64 v. 4/65 and 3/65). The sponsor attributed the increase to the greater longevity of HD M compared to control; however, the increase is statistically significant even after adjustment for survival, and the 17.2% incidence exceeds the 1.4 – 10.0% historical control range reported by [redacted] Survival of HD M exceeded control from approximately 17 months onward, which may reflect the decreased BW gain that occurred at the HD (BW's in HD M and F at the end of the study were 20 and 33% less than control, respectively). The excessive decrease in BW gain at the HD makes it difficult to interpret the increase in histiocytic sarcomas seen in MD M (4/65 v. 1/65 and 1/65); a similar increase did not occur in HD M, but the decreased BW gain at the HD may have decreased tumor expression. The 6.2% incidence at the MD did not exceed the 1.4 – 7.1% historical control incidence reported by [redacted] Non-neoplastic changes observed in HD M included increased incidences of eosinophilic foci in the liver, follicular cell hyperplasia in the thyroid and *pars distalis* hyperplasia in the pituitary. There were also a few changes indicative of improved general health in HD M and F, likely related to the decreased BW gain observed at the HD. The incidences of hepatic periportal vacuolation, adrenal cortical vacuolation, chronic nephropathy, testicular periarteritis, testicular tubular atrophy and mammary gland fibroadenoma were decreased in HD M and/or F.

The decreased BW gain at the HD may have compromised tumor expression, making the MD of 15 mg/kg the highest dose from which tumor data can be reliably evaluated. On a mg/m^2 basis this dose is approximately equal to the proposed maximum recommended daily dose of 2 x 80 mg. The plasma levels achieved at this dose were approximately 20% of the Cmax achieved in humans given an 80 mg dose. No AUC estimations were made in this study; however, extrapolating linearly from results in the dose range-finding study (100, 200, 300 mg/kg), the AUC achieved in M and F rats at 15 mg/kg is predicted to be approximately equal to the 3000 ng.h/ml exposure achieved in humans at the proposed maximum recommended daily dose. The AUC extrapolated for the 75/50 mg/kg dose is approximately 2 times the exposure achieved in humans at the proposed maximum recommended daily dose.

In the 2 year dietary study in mice (20, 90, 400 mg/kg), the incidence of hepatocellular adenoma was increased in HD M (12/50 v. 7/50 and 2/50), with the increase being in eosinophilic, not basophilic, adenomas. Other changes observed in the liver at the HD were increased incidences of foci of cellular alteration, single cell necrosis, pigmentation, and centrilobular changes defined as hepatocyte hypertrophy, karyomegaly and heterogeneous cytoplasm. Although hepatocellular adenoma is a common tumor type in mice, the increased incidence in HD M was clearly drug-related, particularly in view of the concomitant increased incidence in foci of cellular alteration. Also increased in HD M was the incidence of harderian gland adenoma (6/50 v. 3/50 and 0/50), but the increase is equivocal given that this is a fairly common tumor type and the incidence was only doubled at the HD relative to one of the control groups. The incidence at the HD is within the historical control range reported by [redacted] but is slightly outside that reported by Pfizer. The incidence of harderian gland adenoma was also increased in F (3/50, 2/50 and 3/50 at the LD, MD and HD, respectively), owing to a 0/50

occurrence in controls, but the increase was not statistically significant and the incidences fell within the historical control range reported by [redacted].

Dose selection for the mouse carcinogenicity study appears adequate based on the decrease in BW gain that began early in the study and resulted in terminal BW's that were 5 and 13% less than control for HD M and F, respectively. The AUC determined in the 3 month range-finding study (50, 100, 200, 400 mg/kg) for the 400 mg/kg dose was 7 times the 3000 ng.h/ml exposure achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg. The AUC determined for the 100 mg/kg dose, which is similar to the 90 mg/kg NOAEL in the carcinogenicity study, was 3 times the the exposure achieved in humans at the proposed maximum recommended daily dose. The only other available toxicology data in mice is that a gavage dose of 1000 mg/kg is lethal.

[redacted]

Draft Labeling

[redacted]

2 page(s) of revised draft labeling has been redacted from this portion of the review.

RECOMMENDATION

NDA 21-016 is approvable with respect to the pharmacology/toxicology portion provided that the sponsor agrees to complete a fertility study Phase IV and to revise the labeling (specific labeling recommendations are given in the Summary and Evaluation).

The doses selected for the fertility study submitted in the NDA (5, 15, 50 mg/kg) were too low as indicated by the lack of reproductive or general toxicity. As justification for dose selection the sponsor cited the decreased body weight gain observed at 100 mg/kg in the rat embryofetal development study and the thyroid follicular hypertrophy observed at 100 mg/kg in a 1 month general toxicity study (no. 97075). The latter effect does not define an MTD and, therefore, should not be used to limit dosing. The body weight gain deficit observed in the embryofetal development study is likely specific to the pregnancy status of the females during dosing, as it did not occur in the 1 month general toxicology study. Toxicokinetic data were not collected in the fertility study, but results generated in the 6 month general toxicology study indicate that the AUC's in M and F rats given 50 mg/kg are only 1.4 and 2.8 times that achieved in humans given the proposed maximum recommended daily dose of two 80 mg tablets.

It is noted that the sponsor has already agreed to conduct an abbreviated peri- and post-natal study. The peri- and post-natal study submitted to the NDA did not include an assessment of learning and memory in F1 pups, a test generally performed on drugs designed to treat migraine, for which the patient population is largely women of child bearing potential. In response to our January 27, 1999 letter request, the sponsor submitted a protocol and revisions on February 8 and 25, 1999, respectively, in which the sponsor communicated its intention to commence the study on March 9, 1999.

/S/

Robin A. Huff, Ph.D.

cc: NDA21016
HFD-120 /S/ 8/2/99
/G. Fitzgerald
/R. Huff
/L. Chen

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

NDA 21-016

EVALUATION OF REPRODUCTIVE TOXICOLOGY STUDIES

Sidney J. Stolzenberg, PhD
November 16, 2000

NDA AMENDMENT: N-(AZ) SUBMISSION DATED: 6/1/00
CENTER RECEIPT DATE: 6/2/00
REVIEWER RECEIPT DATE: 7/13/00

SPONSOR: Pfizer Central Research
Groton, CT 06340

DRUG: REPLAX™ (Eletriptan hydrobromide) tablets

Background: In the Initial NDA Review dated 6/25/99, the pharm-tox reviewer for this NDA requested that the fertility study be repeated. The doses that had been selected for Study No. 94073, the previous fertility study (5, 15 and 50 mg/kg/day), were too low. They were also asked to repeat the peri- and post-natal study ((Study No. 96016/96017) because the learning and memory assessment of the F_1 generation had not been included. Sponsor agreed to do these studies as a Phase IV commitment for this NDA. This submission contains the two study reports.

1. Fertility and Early Embryonic Study in Rats

Study No: 99105

Performing Laboratory: Pfizer
Centre de Recherche
Ambroise Cedex, France

Dates Performed: Dosing started on 11/22/99, final sacrifice of males on 1/25/00

Quality Assurance: A statement of compliance with GLP is included.

Doses: 0 (control), 50, 100 and 200 mg/kg/day (dose level expressed in terms of base). The dose volumes were 10 mL/kg, based on individual body weight. Vehicle used was 0.5% aqueous carboxymethylcellulose and 0.1% Tween 80.

Animals: Sprague-Dawley Crl:CD (SD) IGS-BR, 20/sex/group, were used. Males were 7 weeks old and mean body weight was 255 g, females were 9 weeks old and mean body weight was 237 g at the beginning of the treatment period.

Procedure: Exactly the same as for Study No. 94073, except the doses of eletriptan hydrobromide (Lot No. R218) were higher, as previously agreed (See Initial Pharmacology

Review by R. Huff, Ph.D., dated 6/25/99). The duration of treatment was 64 days for males and 22-35 days for females, depending on time to mate.

Results: (limited to mortality and drug-related effects)

Mortality: At 50 mg/kg/day, 2 males; one on treatment Day 18 with dyspnea and noisy respiration noted on Days 17 and 18, and one "without unusual clinical signs" was sacrificed in moribund condition on Day 18. Cause of death in both animals was unknown. Since 1 of the males was sacrificed before mating (Day 18), the female of the mating pair was also sacrificed.

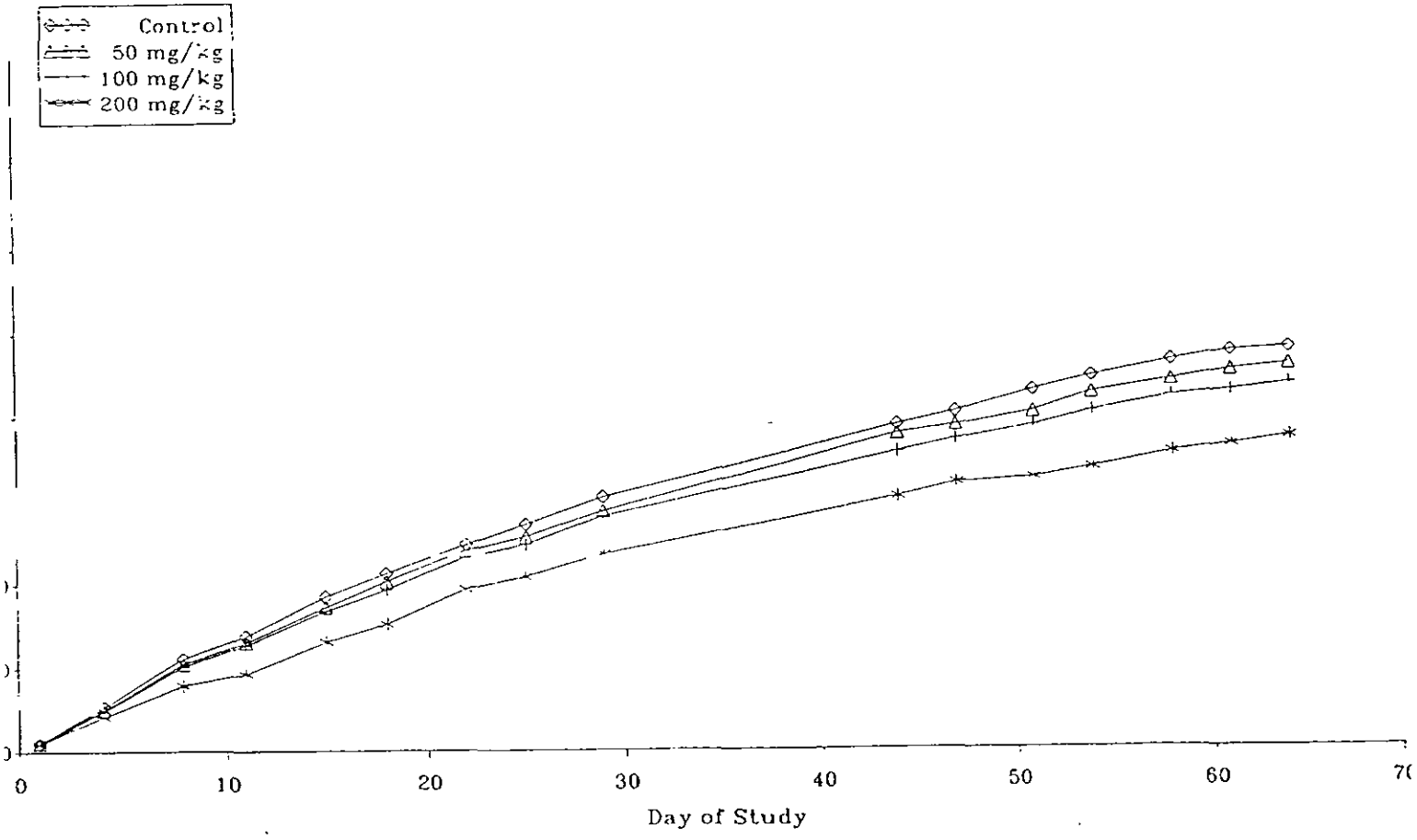
Clinical Signs: All treated animals had salivation (transient). A total of 5 high dose females had treatment related clinical signs for periods of 24-48 hours, including dyspnea, (4/20) and noisy respiration(4/20).

Body Weight: In males, the decreases in mean body weight compared to controls were statistically significant only at high dose, starting on Day 8 of treatment. In females prior to pregnancy, the decreases in mean body weight compared to controls were statistically significant at high dose starting on Day 8 of treatment. In pregnant females, even though there was an initial dose related decrease in body weight at mid and high doses compared to controls during the first 7 days of pregnancy, there was a dose related increase in body weight compared to controls from gestation days 7 to 14. There were also dose-related decreases in food consumption compared to controls associated with the decreases in body weight. See pages 3 to 5.

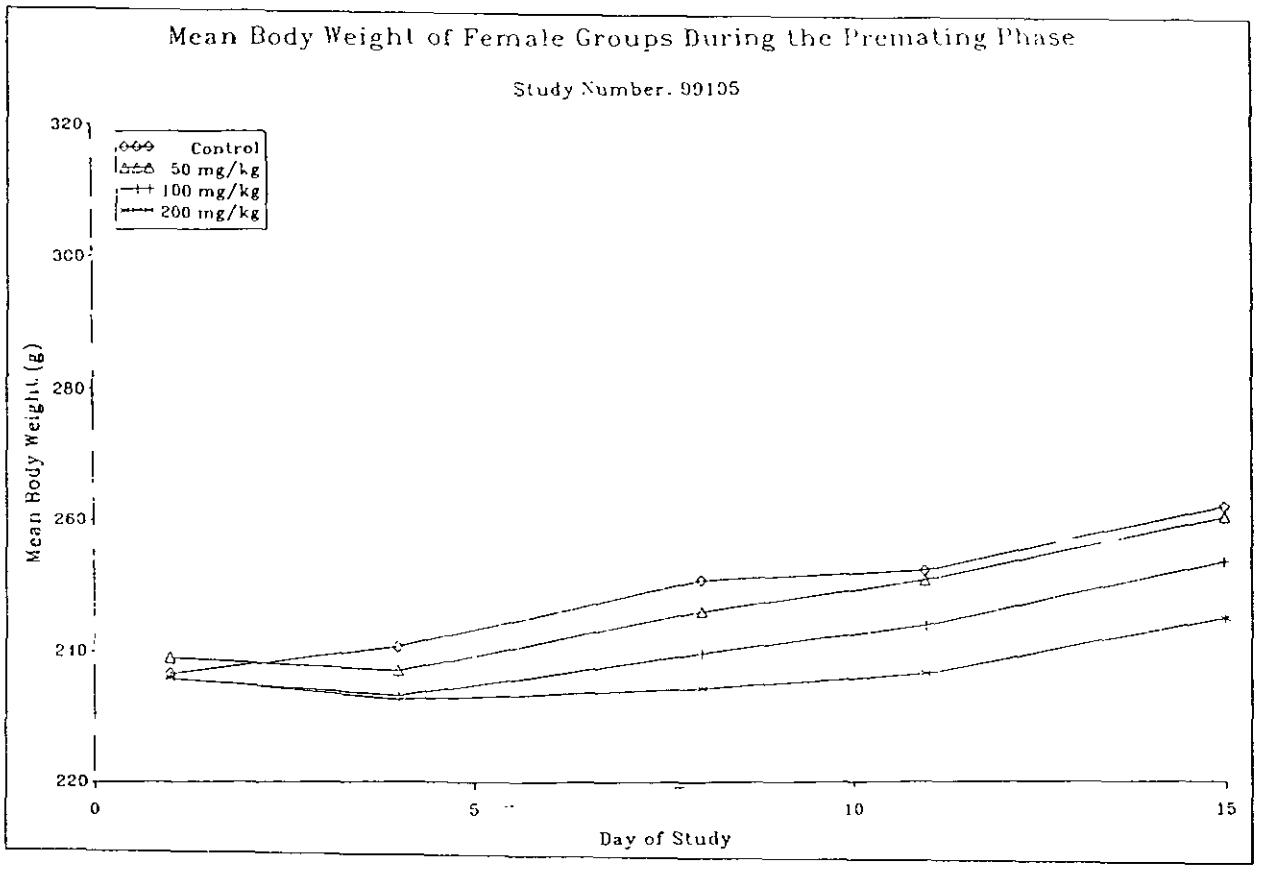
Estrous Cycles and Reproductive Parameters: At high dose, length of the estrous cycles were increased due to an increase in duration of estrus There were no effects on fertility of males or females, but there were dose-related decreases in mean numbers of corpora lutea per dam, associated with decreases in mean numbers of implants and viable fetuses per dam, suggesting a partial inhibition of ovulation. At the high dose, the decreases in numbers of corpora lutea, implants and viable fetuses were all below historical control range. (See tables on page 6.)

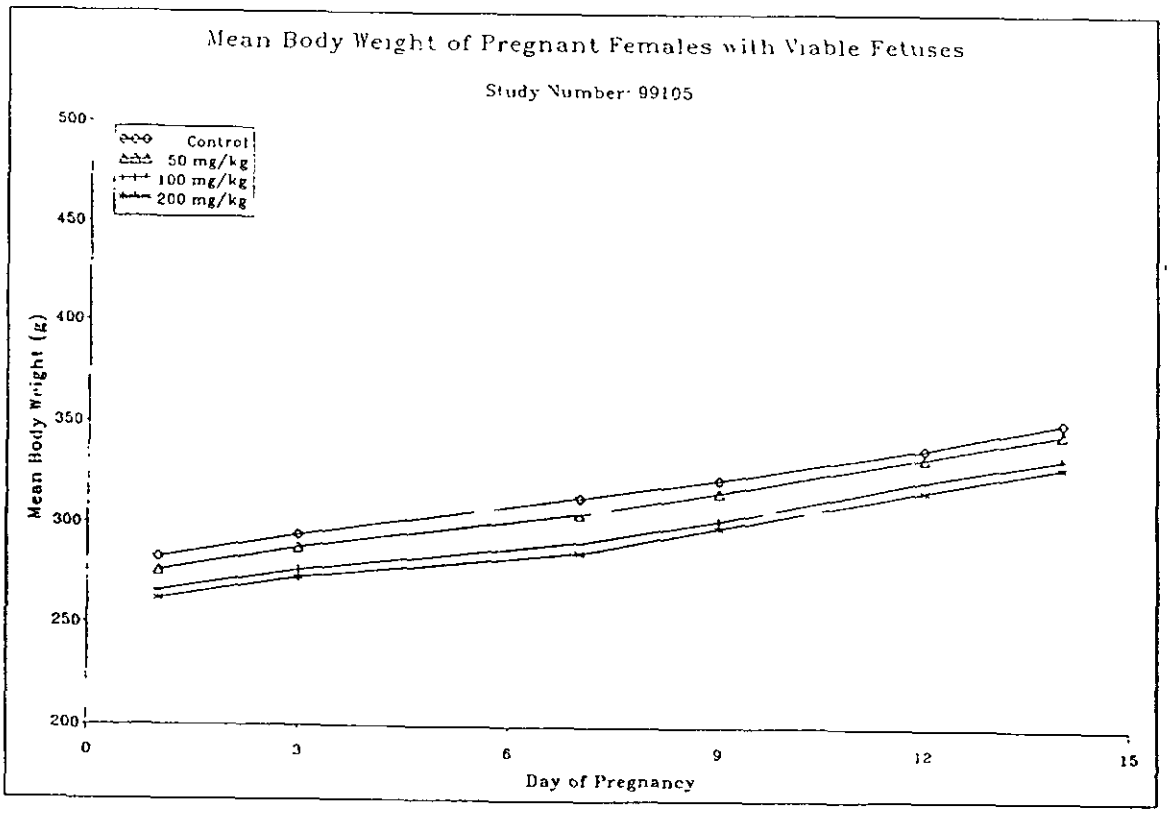
Mean Body Weight of Male Groups

Study Number: 99105



g period: days 30-43


Mean Body Weight of Female Groups During the Premating Phase
Study Number. 99105
Control
50 mg/kg
100 mg/kg
200 mg/kg
Mean Body Weight (g)
320
300
280
260
240
220
0
5
10
15
Day of Study


Mean Body Weight of Pregnant Females with Viable Fetuses
Study Number: 99105
Control
50 mg/kg
100 mg/kg
200 mg/kg
Mean Body Weight (g)
500
450
400
350
300
250
200
0
3
6
9
12
15
Day of Pregnancy

Decreases in mean body weight of males
(% change from controls)

	Premating phase		"Mating phase"		
Day in the phase:	8	29	15	25	35
Day of study:	8	29	44	54	64
50 mg/kg	1.1	2.1	1.2	2.1	2.0
100 mg/kg	1.6	2.8	3.7	4.4	4.4
200 mg/kg	5.4*	8.4**	9.8***	11.5***	10.8***

*, **, ***: statistically significant at p = 0.05, 0.01 and 0.001, respectively.

Decreases in mean body weight of females
(% change from controls)

	Premating phase		Gestation phase		
	Day 8	Day 15	Day 1p.i.	Day 7p.i.	Day 14p.i.
50 mg/kg	1.9	0.6	2.4	2.6	1.5
100mg/kg	4.4*	3.2	6.0**	7.2***	5.0*
200mg/kg	6.5**	6.5**	8.0***	9.4***	6.2***

*, **, ***: statistically significant at p = 0.05, 0.01 and 0.001, respectively.

Changes in mean body weight gain of pregnant females
(% change from controls)

	Days 1-7p.i.	Days 7-14p.i.
50 mg/kg	- 4.4	+ 7.5
100mg/kg	- 18.9 *	+ 13.7*
200mg/kg	- 22.3 *	+ 23.4*

*: statistically significant at p = 0.05.

Estrus cycle changes

	Control	50 mg/kg	100 mg/kg	200 mg/kg
No. of females evaluated for estrus cycle length [a]	20	20	20	16
Mean estrus cycle length (days)	4.2	4.1	4.2	4.9***
Total occurrence of estrus	75	69	68*	48***
No. of females evaluated for duration of estrus [b]	20	20	20	17
No. of estrus of 1 day duration	60	56	50	26
No. of estrus of 2 days duration	2	3	8*	11***

*, *** . statistically significant at p = 0.05 and 0.001, respectively.

[a] Among the 20 females examined at 200 mg/kg, 4 females (F808, F812, F818 and F819) could not be evaluated for the estrus cycle length (no full cycle occurred during the premating period).

[b] Among the 20 females examined at 200 mg/kg, 3 females (F808, F812 and F819) could not be evaluated for the duration of estrus (estrus occurred at the beginning or at the end of the premating period and lasted less than 3 days).

Fertility and reproductive parameters

(See Tables 9-10, pages 44-47 and Individual Data Appendix, pages 145-154)

Status of females

	Control	50 mg/kg	100 mg/kg	200 mg/kg
No. of females caged with males	20	20	20	19 [a]
No. of females mated	20	20	20	19
No. of pregnant females	19	19	20	19
No. of non-pregnant females	1	1	0	0

[a] F804 was sacrificed since the mating pair (M304) died before mating

Mean reproductive parameters

	Control	50 mg/kg	100 mg/kg		200 mg/kg	Range of Historical control data base [b]
			With F718	F718 excluded [a]		
No. of corpora lutea	17.7	16.9	16.5*	16.5*	15.7***	16.1-17.5
No. of implants	16.3	15.2**	15.0***	15.0***	13.2***	14.5-16.1
No. of viable fetuses	15.7	14.5*	13.7***	14.2***	12.3***	13.4-15.2
Pre-implantation loss, %	7.3	9.5	8.3	8.3	14.0	6.4-10.1
Post-implantation loss, %	3.7	4.3	8.4	5.2	6.8	5.8-7.6

*, **, ***: statistically significant at p = 0.05, 0.01 and 0.001, respectively.

[a] F718 had an exceptionally high post-implantation loss (68.8%) which biased the group mean.

[b] 3 studies between 1997 and 1999 with control groups of 19-20 females.

2. **Pre- and Post-natal Development Study in Rats: Assessment of Learning and Memory of F_1 Pups**

Study No: 99027

Performing Laboratory: Pfizer
Centre de Recherche
Ambroise Cedex, France

Dates Performed: Dosing started on 3/22/99, terminated on 7/22/99 after completion of the passive avoidance test.

Quality Assurance: A statement of compliance with GLP is included.

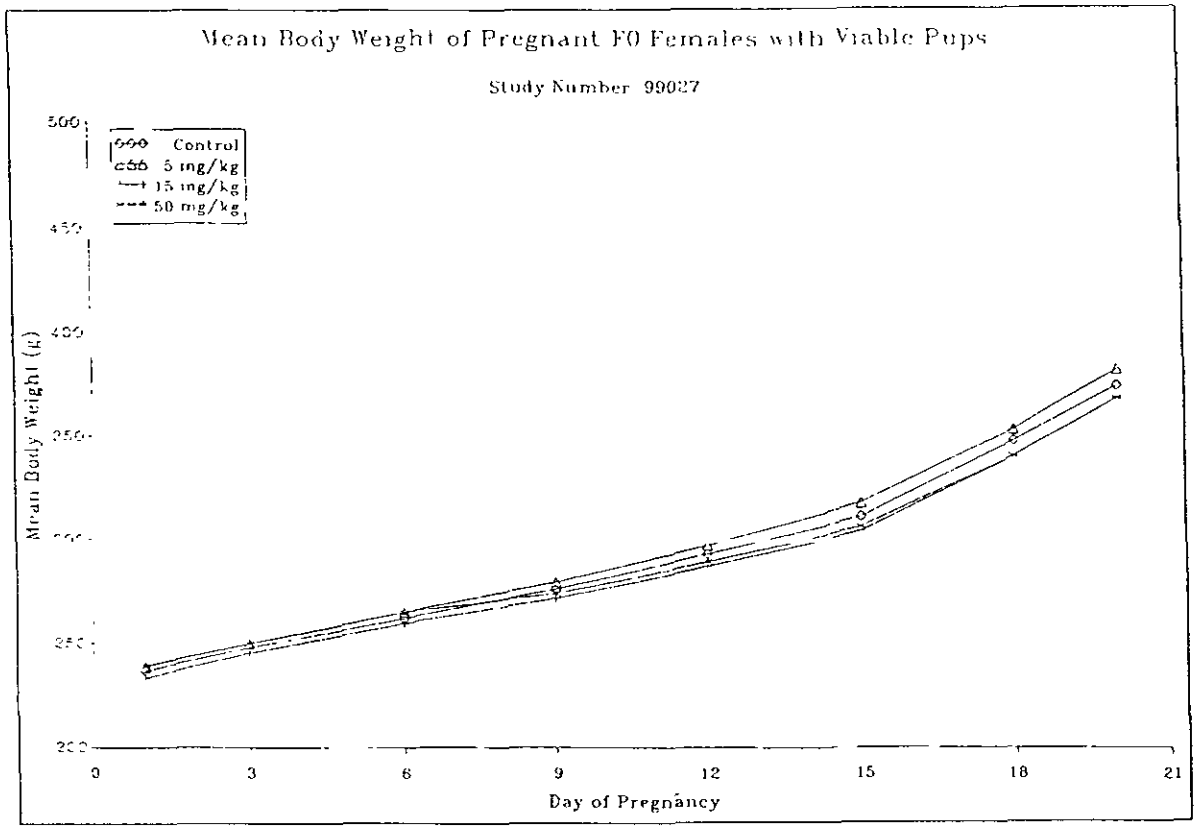
Doses: 0 (control), 5, 15 and 50 mg/kg/day (expressed in terms of base). Dose volumes were 10 mL/kg, vehicle used was 0.5% aqueous carboxymethylcellulose and 0.1% Tween 80.

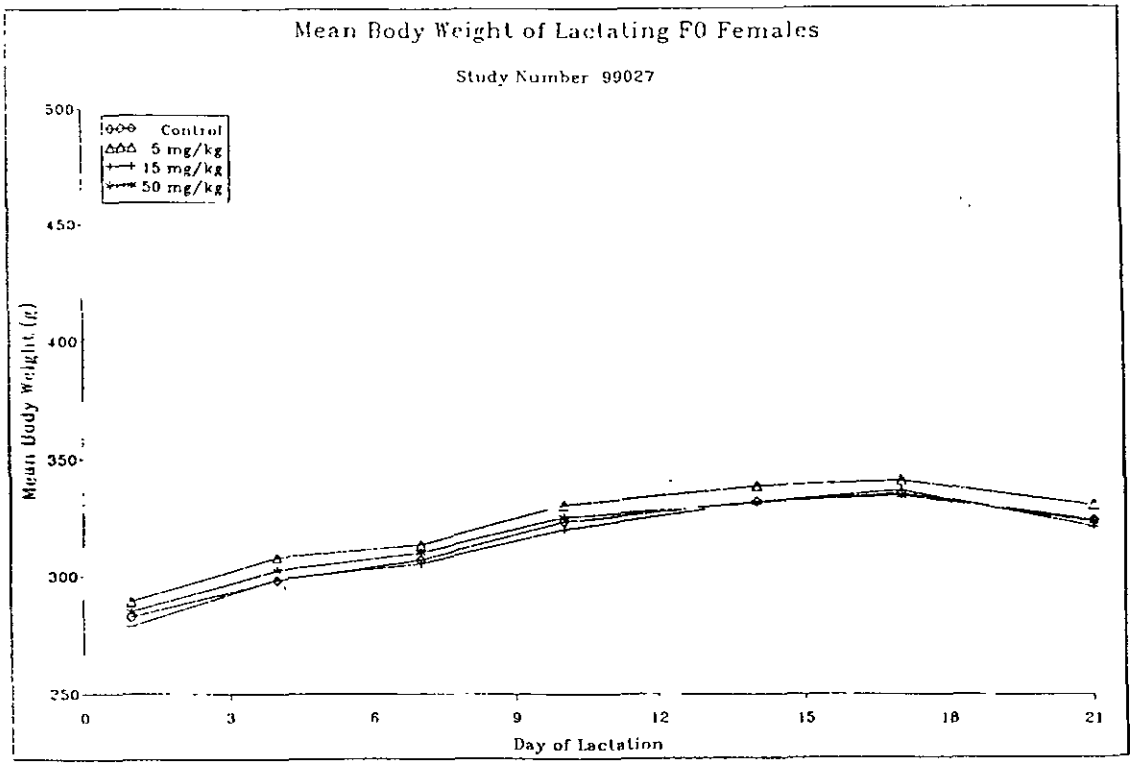
Animals: Sprague-Dawley Crl:CD (SD) IGS-BR female rats, 28/sex/group, 8 to 15 weeks old, with a mean body weight of 237 g at the beginning of the treatment period, were used.

Procedure: Initially, the procedure was exactly the same as for Study No. 96016/96017 (See Initial Pharmacology Review by R. Huff, Ph.D., dated 6/25/99). The dams were treated by oral gavage with eletriptan hydrobromide Lot No. R203 from GD 6 to PPD 20 (36 consecutive days). All F_1 pups were examined for eyelid opening each day from PPD 11 to PPD 19, for righting reflex each day from PPD 14 to PPD 21. After weaning, 2 pups/sex/litter were randomly selected for further evaluation, including vaginal opening starting on PPD 28 or for separation of prepuce starting on PPD 37. One pup/sex/litter was evaluated for learning by means of the Cincinnati water maze test each day from PPD 66 to PPD 78, the second pup/sex/litter was evaluated for the passive avoidance test each day between PPD 80 and PPD 84. The experiment was terminated after completion of the passive avoidance tests, which was sufficient to satisfy our request for repetition of the study.

Results: **F_0 Males and Females** (Limited to drug related effects

Body Weight and Body Weight Gain of Dams: The investigators claim that there were decreases in mean body weight gain at mid (9%) and high (16%) doses relative to controls, between GD 6 and 15. However, there were no statistically significant differences in mean body weight or body weight gains between treated and control groups.


Mean Body Weight of Pregnant F0 Females with Viable Pups
Study Number 99027
Control
5 mg/kg
15 mg/kg
50 mg/kg
Mean Body Weight (g)
500
450
400
350
300
250
0
3
6
9
12
15
18
21
Day of Pregnancy


Mean Body Weight of Lactating F0 Females
Study Number 99027
Control
5 mg/kg
15 mg/kg
50 mg/kg
Mean Body Weight (g)
500
450
400
350
300
250
0
3
6
9
12
15
18
21
Day of Lactation

Assessment of Learning and Memory of F_1 Pups

There were no landmark developmental effects, including, eyelid opening, air righting reflex, and preputial separation in males and vaginal opening in females (see below). Trials 11 and 12 for the Cincinnati water maze and passive avoidance tests are not shown in the tables that follow because no effects were evident. There were no increases number of errors in the water maze of treated compared to control groups, except at trial 6 and 9 (PPD 72 and 75), but we consider these effects as sporadic because they were associated with an unusually low number of errors in controls at those time periods, there was no meaningful effect on time to exit water and the effect would have been evident sooner if it was a real effect. There were no significant effects in the passive avoidance test.

SY TABLE OF TIMES (days) FOR ATTAINMENT OF DEVELOPMENTAL LANDMARKS IN F_1 PUPS

MALES

		Control	5 mg/kg	15 mg/kg	50 mg/kg
ng	Mean	14.80	14.64	14.62	14.67
	S.D.	0.52	0.77	0.67	0.70
	N	27	28	28	27
reflex	Mean	18.57	18.13	18.68	18.45
	S.D.	0.86	1.21	0.97	1.08
	N	27	28	28	27
aration	Mean	41.61	41.68	41.43	41.31
	S.D.	1.68	1.42	1.32	1.29
	N	27	28	28	27

SUMMARY TABLE OF TIMES (days) FOR ATTAINMENT OF DEVELOPMENTAL LANDMARKS IN F_1 PUPS

FEMALES

		Control	5 mg/kg	15 mg/kg	50 mg/kg
Eyelid opening	Mean	14.58	14.50	14.53	14.57
	S.D.	0.48	0.75	0.70	0.70
	N	27	28	28	27
Air righting reflex	Mean	18.82	18.28	18.76	18.73
	S.D.	1.06	0.94	1.02	0.97
	N	27	28	28	27
Vaginal opening	Mean	33.09	33.02	32.40	32.83
	S.D.	1.83	2.14	1.48	1.92
	N	27	28	29	27

TIME (days) TO EXIT WATER MAZE FOR F$_1$ PUPS

MALES

		Control	5 mg/kg	15 mg/kg	50 mg/kg
Trial 1	Mean	90.7	119.7	106.0	103.2
	S.D.	55.7	83.1	80.9	79.5
	N	27	27	28	27
Trial 2	Mean	70.9	115.8	86.7	75.3
	S.D.	56.8	91.9	70.6	60.1
	N	27	27	28	27
Trial 3	Mean	80.8	85.7	84.6	71.1
	S.D.	66.4	57.4	80.5	63.2
	N	27	27	28	27
Trial 4	Mean	67.0	69.5	57.9	73.0
	S.D.	58.9	45.3	57.5	77.4
	N	27	27	28	27
Trial 5	Mean	61.4	60.7	58.2	78.0
	S.D.	51.5	54.4	55.3	81.1
	N	27	27	28	27
Trial 6	Mean	52.7	69.5	62.5	71.0
	S.D.	52.7	53.6	55.4	71.5
	N	27	27	28	27
Trial 7	Mean	288.6	253.7	261.8	279.1
	S.D.	40.7	58.7	62.1	55.7
	N	27	27	28	27
Trial 8	Mean	262.5	251.5	243.8	242.5
	S.D.	68.3	80.9	100.5	94.3
	N	27	27	28	27
Trial 9	Mean	155.4	167.2	237.1**	184.1
	S.D.	99.3	121.7	104.1	110.3
	N	27	27	28	27
Trial 10	Mean	111.6	141.9	141.0	140.6
	S.D.	105.7	126.6	116.0	126.3
	N	27	27	28	27

TIME (days) TO EXIT WATER MAZE FOR F$_1$ PUPS

FEMALES

		Control	5 mg/kg	15 mg/kg	50 mg/kg
Trial 1	Mean	96.1	110.1	100.9	107.3
	S.D.	55.7	66.4	59.9	58.7
	N	27	28	27	27
Trial 2	Mean	75.1	78.6	82.5	70.7
	S.D.	51.9	58.0	59.7	58.5
	N	27	28	27	27
Trial 3	Mean	72.0	61.5	71.2	80.7
	S.D.	52.0	41.9	48.4	72.1
	N	27	28	27	27
Trial 4	Mean	55.4	59.3	55.1	65.2
	S.D.	39.5	30.4	37.9	65.8
	N	27	28	27	27
Trial 5	Mean	48.6	72.8	54.1	53.5
	S.D.	31.6	60.0	27.3	26.7
	N	27	28	27	27
Trial 6	Mean	61.9	61.3	55.4	54.4
	S.D.	49.3	32.0	40.6	38.4
	N	27	28	27	27
Trial 7	Mean	286.5	267.5	287.8	276.8
	S.D.	46.0	67.2	48.0	58.3
	N	27	28	27	27
Trial 8	Mean	258.6	193.9**	243.7	228.9
	S.D.	62.3	107.4	104.9	89.2
	N	27	28	27	27
Trial 9	Mean	218.9	158.1*	225.1	213.6
	S.D.	106.6	109.4	96.4	97.0
	N	27	26	27	27
Trial 10	Mean	141.7	124.2	133.5	135.5
	S.D.	101.9	112.3	128.4	109.8
	N	27	28	27	27

NUMBER OF ERRORS IN WATER MAZE FOR F1 PUPS

MALES

		Control	5 mg/kg	15 mg/kg	50 mg/kg
Trial 1	Mean	11.5	13.4	11.6	12.5
	S.D.	5.9	7.3	6.5	8.1
	N	27	27	28	27
Trial 2	Mean	6.2	9.9	6.7	7.8
	S.D.	5.2	8.2	5.9	5.5
	N	27	27	28	27
Trial 3	Mean	6.9	7.7	6.0	6.0
	S.D.	5.3	5.4	6.4	4.7
	N	27	27	28	27
Trial 4	Mean	4.3	5.6	2.1*	4.7
	S.D.	4.6	5.2	3.0	4.4
	N	27	27	28	27
Trial 5	Mean	3.6	3.8	3.0	4.9
	S.D.	2.6	5.1	3.1	5.0
	N	27	27	28	27
Trial 6	Mean	1.6	3.8	3.0	3.9**
	S.D.	2.3	4.7	3.4	3.0
	N	27	27	28	27
Trial 7	Mean	25.2	23.3	25.1	28.4
	S.D.	9.6	8.6	10.8	7.6
	N	27	27	28	27
Trial 8	Mean	13.1	13.5	11.5	15.9
	S.D.	6.7	9.6	9.2	9.2
	N	27	27	28	27
Trial 9	Mean	8.3	10.0	13.1*	11.5*
	S.D.	7.4	10.8	9.1	8.7
	N	27	27	28	27
Trial 10	Mean	3.5	4.6	5.3	5.5
	S.D.	4.6	7.7	7.7	9.5
	N	27	27	28	27

NUMBER OF ERRORS IN WATER MAZE FOR F1 PUPS

FEMALES

		Control	5 mg/kg	15 mg/kg	50 mg/kg
Trial 1	Mean	12.6	14.0	13.0	15.1
	S.D.	8.3	7.6	7.7	8.1
	N	27	28	27	27
Trial 2	Mean	9.8	8.3	9.2	7.3
	S.D.	6.6	5.6	7.3	5.5
	N	27	28	27	27
Trial 3	Mean	9.1	6.5	7.7	6.2
	S.D.	7.1	5.3	6.7	7.0
	N	27	28	27	27
Trial 4	Mean	5.1	5.8	4.6	5.6
	S.D.	5.3	5.6	4.5	4.5
	N	27	28	27	27
Trial 5	Mean	3.6	5.1	4.7	4.5
	S.D.	3.2	5.7	3.6	3.6
	N	27	28	27	27
Trial 6	Mean	4.4	4.2	4.1	4.1
	S.D.	4.2	3.6	4.5	4.5
	N	27	28	27	27
Trial 7	Mean	32.4	28.0	30.7	29.6
	S.D.	9.2	9.6	9.6	10.4
	N	27	28	27	27
Trial 8	Mean	19.5	13.5	16.1	15.8
	S.D.	8.5	10.1	9.0	9.0
	N	27	28	27	27
Trial 9	Mean	19.0	12.3	20.9	16.2
	S.D.	12.3	11.4	10.9	10.2
	N	27	28	27	27
Trial 10	Mean	8.0	6.5	7.0	7.3
	S.D.	8.6	6.9	7.5	6.5
	N	27	28	27	27

SUMMARY TABLE OF TIMES (days) FOR PASSIVE AVOIDANCE IN F1 PUPS

			Control	5 mg/kg	15 mg/kg	50 mg/kg
MALES	Trial 1	Mean	19.6	23.9	29.9	36.2
		S.D.	14.2	15.9	21.1	38.0
		N	26	28	27	26
	Trial 2	Mean	155.6	155.4	167.3	160.3
		S.D.	58.5	58.7	45.8	51.6
		N	26	28	27	26
FEMALES	Trial 1	Mean	18.8	21.4	18.8	26.2
		S.D.	16.3	16.4	9.7	16.2
		N	27	28	28	26
	Trial 2	Mean	130.1	124.4	117.5	135.1
		S.D.	76.4	71.6	74.3	75.5
		N	26	26	29	26

SUMMARY AND EVALUATION

In the fertility and early embryonic study, there was an increase in length of the estrous cycle at the high dose (200 mg/kg/day) due to an increase in duration of estrus. There were no effects on fertility of males or females, but there were dose-related decreases in mean numbers of corpora lutea per dam, resulting in decreases in mean numbers of implants and viable fetuses per dam. This suggests a partial inhibition of ovulation by eletriptan.. There were no biologically meaningful effects in F_1 offspring in the learning and memory assessment tests.

CONCLUSION

The sponsor has repeated the fertility study and the learning and memory assessment of F_1 rats in the peri- and post-natal study as a Phase 4 requirement, in accordance of our previous request. The Pharmacology and Toxicology requirements for this NDA have been fully satisfied.

/S/
Sidney Stolzenberg, Ph.D.

cc:
HFD-120 Division File
HFD-120/LChen
HFD-120/GFitzgerald /S/ 11/22/00
HFD-120/AOliva
HFD-120/SStolzenberg
NDA21-016.rv4.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA:	21-016
DRUG NAME:	Relpax ® (Eletriptan)
INDICATION:	Migraine
SPONSOR:	Pfizer
STATISTICAL REVIEWER:	Sharon Yan
DATE OF DOCUMENT:	June 27, 2002

DISTRIBUTION:

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Eric Bastings, M.D., Clinical Reviewer
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