CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20763

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
— Original Review of NDA 20-763

Drug: **Naratriptan**, tablets

Sponsor: GlaxoWellcome
Research Triangle Park, NC 27709

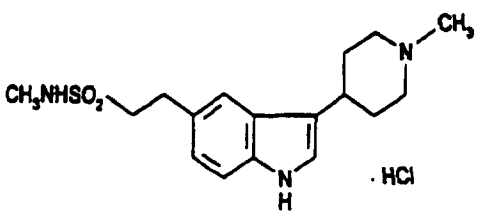
Review Date: 5/30/97

Reviewer: Robin Huff

Class: 5HT1 agonist

Indication: migraine

Structure:



Chemical Name: N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride

Molecular Formula: $C_{17}H_{25}N_3O_2S$ HCl

MW: 371.9

Related INDs/NDAs IND
NDA 20-080, approved (Sumatriptan, injection)
NDA 20-132, approved (Sumatriptan, tablet)

Table of Contents

I. Absorption, Distribution, Metabolism, and Excretion (ADME)

Most ADME data has been reviewed in the attached IND review, but an additional study was submitted that examined the metabolism of Naratriptan after oral administration to mice, rats, rabbits, dogs and humans (study BDRR/96/0008). Rabbits (females only) and dogs were given a single oral dose of 1 mg/kg radiolabeled Naratriptan, mice, Charles River Wistar rats, and Han Wistar rats were given a single oral dose of 10 mg/kg radiolabeled drug, and humans were given either 1 or 2.5 mg unlabeled Naratriptan. The disposition of radiolabel amongst parent and metabolites in the plasma (1 hr) and urine (0 - 24 hr) of the various animal species is shown in the sponsor-supplied table below. Naratriptan accounted for all or most of the radiolabel in plasma, except in rabbits. Multiple metabolites were found in the urine, although unchanged parent still accounted for the majority of radiolabel, except in the rabbit. Because few metabolites were found in plasma compared to urine, it was concluded that when metabolites are formed they are rapidly excreted. The human data was not quantitative, but parent, N-oxide, and piperidone were described as being prominent in plasma, with parent being the major component. Various other oxidation and demethylation structures were also detected. Components detected in the urine were generally the same as those detected in plasma, with parent, N-oxide, and piperidone dominating.

Percentage of GR85548 related material in a chromatograph of a plasma or urine extract.										
	Plasma			Urine						
Species	GR85548	N-oxide	α-OH	GR85548	N-oxide	α-OH	des-Me	+32	des-Me α-OH	Piperi-dine one
Dog(m)	90	10		58	34	0.9	0.7	5.8		<1
Dog (f)	89	11		47	28	1.1	0.9	3.7		<1
Rabbit	100/0[a]		0/100[a]	27	<1	41			28	
Mouse	100			80	3.1	6.4	2.8			2.6
Rat	100			87	1.5	4.9	1.6			2.2

[a] - In a pair of rabbits in this study the plasma from one animal contained only the parent, while plasma from the other animal contained only the α-hydroxy metabolite.

II. Chronic Toxicology

APPEARS THIS WAY
ON ORIGINAL

A. Dogs, 12 months oral (D13682) GLP, QA

Beagle dogs - 1.0, 2.25, 5 mg/kg (batches F92/138A, F92/194A, F93/023A)
4/s/gr + 2/s for 44 day recovery (C and HD) and 3/s for 6 mo interim kill (C and HD)

In order to achieve the 2.25 and 5 mg/kg doses, animals received escalating doses during the first week. A preliminary study had shown that tolerance develops to repeated doses, allowing doses to be achieved that could not be tolerated in naive dogs.

Mortality — 2 HD M were killed for humane reasons on days 270 and 290 after repeated convulsive episodes.

Clinical Signs — Pupil dilation, pink ears, and pink gums were observed frequently in all treated groups. In all treated groups, corneal stippling and hind leg stiffness were observed during the first 2 weeks and aggressive behavior and vocalization were observed throughout the study. Salivation was seen in HD dogs and occasionally in LD and MD dogs. Some MD and HD dogs were "difficult to wake" on a single occasion early in the study.

Repeated convulsions occurred in 2 HD M as of day 245. One dog experienced fits lasting 2 - 3 min on 3 - 4 different days and was autopsied after the last episode. In addition to convulsing on multiple occasions, the second dog deteriorated on day 289; he experienced multiple convulsions, was unable to stand, and seemed unaware of his surroundings. The dog was unconscious and displaying continuous muscle movements when autopsy was ordered the following day.

Body Weight — BW was decreased 5 - 9% in all treated groups during week 1 of the study. LD animals recovered BW losses from day 21 (males) and day 77 (females). MD F and HD M and F recovered losses by 6 months, but MD M had reduced BW throughout the study. There were no notable changes in food consumption.

Eyes — Indirect ophthalmoscopy following mydriasis performed at 3, 6, 9, and 12 months revealed no treatment-related findings, but corneal stippling was observed during the first 2 weeks of treatment.

Cardio — ECG performed prior to dosing at 3, 6, 9, and 12 months revealed no treatment-related changes.

Neuro Exam — Neurological exams performed at 8 and 12 months in C and HD animals revealed no major neurological deficits. Light and/or blink reflexes were elicited less strongly than normal in some HD animals.

Hematology — Parameters were measured during pretreatment and at 1, 3, 6, 9, and 12 months. Hb, hematocrit, and RBC's were reduced 4 - 14% in MD and HD animals for up to 6 months, but generally recovered by 9 months (the 4 - 5% decrease in RBC's in HD M did not recover). In LD animals, there was no effect on hematocrit, but Hb was reduced in males at 1 month and Hb and RBC's were reduced in females at 3 months. Reticulocytes were decreased 47% in HD F at 1 month and 18% in HD M and 30% in LD F at 9 months. Activated partial thromboplastin time was increased 6 - 12% in MD F at 1, 3, and 6 months and 14 - 17% in HD F at 3 and 6 months.

Clinical Chem — Parameters measured during pretreatment and at 1, 3, 6, 9, and 12 months showed only relatively minor changes. AP was increased 60 - 80% relative to pretreatment values in 2/6 HD F at 9 months, with values being outside the control range. One of these animals had similar increases from 3 - 12 months. ALT was increased 3.5 and 7.8X at 6 and 9 months in the HD M that experienced convulsions and severe deterioration. Creatinine was decreased 14% at 1 month in HD F.

Urinalysis — Parameters measured during pretreatment and at 1, 3, 6, 9, and 12 months showed no treatment-related effects.

Plasma Studies — Blood samples were taken from 2/s/gr during week 1, and at 6 and 12 months. Samples were taken at 5, 15, and 30 min, and 1, 2, 4, 6, 8, 10, 12, and 24 hrs after dosing. There were no obvious differences related to sex or day of measurement. Cmax and AUC increased in an approximately dose linear manner with the average Cmax being 300, 655, and 1563 ng/ml and the average AUC being 1180, 2510, and 5780 ng.h/ml for LD, MD, and HD animals, respectively. Convulsions were associated with plasma levels 124X the human Cmax and 59X the human AUC following a single 2.5 mg dose. The NOEL for convulsions was associated with a Cmax and AUC that were 52 and 26X, respectively, the human values attained after a single 2.5 mg dose. Tmax ranged from 5 min to 2 hrs, and was generally 15 - 30 min. Elimination $t_{1/2}$ averaged 2.9 hr. No accumulation occurred as indicated by a lack of increase in AUC over time and negligible drug detection at 24 hr (≤ 30 ng/ml at the HD).

Organ Weights — Absolute thymus weight was decreased 47, 26, and 11% below the lowest control value in 3/4 HD F at 12 months. The 47% decrease was associated with a 40% decrease relative to BW, but the other relative values were within the control range.

Pathology — There were no macroscopic findings of concern. Histopathologically, 1 HD M killed at 6 months displayed moderate hypertrophy of the thyroid follicular epithelium that was associated with depletion and mineralization of colloid and microfollicle formation. Thyroid follicular cell adenoma was found in 1 LD F at 12 months. There were no histopathological findings that explained the poor clinical condition of the 2 HD M that were terminated for humane reasons. The dog in the worst condition displayed agonal hemorrhage and focal mucosal necrosis in the stomach.

II. Reproductive Toxicology

A. Rat Segment I, II, and III Combined Study (R13737) GLP, QA

This study has been reviewed in the attached IND review; however, several issues that required further comment are discussed below. While certain deficiencies have been addressed in additional Segment II and III studies, this study is the only Segment I study submitted and it is poorly designed and interpreted for the reasons indicated below.

Charles River Wistar rats - 10, 60, 170, 340 mg/kg p.o. (batches C1993/259/1 and C1893/197/1) 24/s/gr, approximately half killed on GD21 and half allowed to deliver

Males were dosed for 72 days prior to mating, and dosing was continued until termination on day 135 or 136. Females were dosed for 23 days prior to mating and until GD21 if killed on this day or throughout lactation if allowed to deliver. At least 1 M and 1 F from each litter were kept until sexual maturity and were mated within dosage groups. The F1 and F2 generations were evaluated and killed 4 - 7 weeks post partum.

A major deficiency is the inadequate number of females allocated to each group. ICH stipulates that 16 - 20 dams be used per group per study segment in order to achieve reasonable sensitivity. In the current study, 22 - 24 females per group were subsequently divided in half between the Segment I/II and Segment III studies. Thus the maximum number per group was 12, and due to a fertility index of < 1, the number of HD dams whose uterine contents were examined was only 10, and the number allowed to deliver was only 9. Of the 9 dams that were to litter, 1 died from a dosing accident on GD20. Of the 8 litters actually delivered, 1 was eaten by day 2 and 2 others died by day 4 (in one of these litters 7/10 pups were already dead on day 2 and may have been stillborn). Thus the initial problem of too few animals was compounded by dam and litter deaths, such that only 5 HD litters survived for evaluation. Because of the small number of HD litters, HD F1 animals were not mated and the effect of the HD on the F2 generation could not be investigated. Furthermore, with respect to the deaths of 2 entire HD litters and the death of 4/12 pups from another HD litter prior to day 4, it is noted that the sponsor presented the median viability index of 1. In fact, the sponsor presented the median for all parameters measured. The median is an inappropriate parameter to use when evaluating a reproductive toxicology study because substantial events can go undetected; means should have been presented.

Among the findings in the Segment I/II part of the study were increased pre-implantation loss in the 60, 170, and 340 mg/kg groups and increased post-implantation loss in the 60 and 340 mg/kg groups. A large number of litters were affected (*e.g.*, 5/10 340 mg/kg litters and 3/10 170 mg/kg litters had preimplantation losses that exceeded control losses). Losses culminated in a 47% decreased number of live fetuses per litter in the 340 mg/kg group as well as a 20% decrease in the birth index and a 34% decrease in the number of live births per litter from dams that were allowed to deliver. In an effort to further investigate the observed pre- and post-implantation loss, treated males from the primary study were mated with untreated females. As in the primary study, insufficient numbers of animals were used, 11 - 12 per group, and only 8 pregnancies resulted in the HD group. In this study, preimplantation loss was again increased in the HD group (28% v. 9% in controls), primarily due to 2 of 8 animals that had losses in excess of 85%. There were no effects of treatment on post-implantation loss. The data suggest that male fertility is impaired at 340 mg/kg and that increased pre-implantation loss may be mediated in part via an effect on the male.

Note: In addition to the use of insufficient numbers of animals, the main study is further compromised by a high background of preimplantation loss which exceeded 31% in 4/12 control animals (33%) in comparison to 4/141 historical controls (3%).

B. Rat Investigational Segment I Study (R20036) GLP, QA

This study was designed to further investigate the increased pre-implantation loss observed in Study R13737.

Charles River Wistar rats - 10, 30, 60, 170, 340 mg/kg p.o. (batch C1893/197/1)
12 F/gr

Female rats were given 10, 30, 60, 170, or 340 mg/kg for 22 days prior to mating and through GD12. C-sections were performed on GD13. As in the above described studies, insufficient numbers of animals were used, 12/group, such that only 8 and 9 pregnancies were evaluated at the 170 and 340 mg/kg doses. The sponsor reports no statistically significant effect of treatment on preimplantation loss and therefore concludes that the effects seen in the previous study cannot be ascribed to effects on the female reproductive tract alone. This conclusion is unwarranted because 1) the study design should have incorporated approximately twice the number of animals per group and 2) preimplantation loss was calculated as total number of losses per group/total number of lutea per group whereas the appropriate parameter to use is loss/litter. Furthermore, there is evidence to suggest that preimplantation loss was increased by 170 and 340 mg/kg treatments. Part of the reason this information was overlooked in the experimental analysis is that 1 animal from each of these groups was sacrificed on day 38 of treatment because there was no evidence of mating. Post-mortem examination showed both animals to be pregnant and to have sustained significant preimplantation losses. When these animals are included in the analysis, whereas the highest control preimplantation loss was 12.5%, 2 animals receiving 170 mg/kg sustained losses of 29 and 62% and 2 animals receiving 340 mg/kg sustained losses of 29 and 44%.

C. Rat Segment II Study (R1386) GLP, QA

D. Dutch Rabbit Segment II Study (L13608) GLP, QA

It is noted that the number of litters examined is less than recommended. Although 17 females per group were mated, due to non-pregnancies and embryonic losses only 11, 9, 13, and 13 litters were examined in the control, LD, MD, and HD groups, respectively. Post-implantation loss was increased at all doses, being 28, 25, and 22% for LD, MD, and HD groups versus 14% for controls (historical control range is 3 - 15%). The sponsor reports an increase only at the MD and HD because the sponsor inappropriately calculated mean loss as total losses per group/total implantations per group, rather than averaging the loss per litter. Maternal toxicity, as evidenced by BW loss, occurred only at the HD of 30 mg/kg.

E. New Zealand Rabbit Segment II Study (L20252) GLP, QA

Unlike in Dutch rabbits, there was no drug-related post-implantation loss in New Zealand rabbits.

F. Rat Segment III Study (R20826) GLP, QA

Charles River Wistar rats - 10, 60, 340 mg/kg p.o. (batch F94/080A)
15 dams/gr

Dams were dosed from GD17 through litter day 22. There was an increased incidence of piloerection in HD dams during pregnancy and lactation. Salivation was also observed in HD dams during lactation. BW gain from GD17 - GD21 was decreased 27% in HD dams subsequent to a 22% decrease in food consumption. A statistically insignificant 16% decrease in BW gain was measured during lactation in HD F; food consumption was decreased 17% during this period.

All dams delivered litters, but the incidence of litters with stillborn pups was increased in the HD group (6/15 v. 1/15 controls), with 1 litter having 10/11 pups stillborn. Pup deaths occurred in the majority of HD litters prior to day 4, with four litters being lost entirely; two MD litters lost five pups each prior to day 4. Consequently, only 11 HD litters could be evaluated for effects on the F1 generation. The decrease in pup viability is not properly reflected in the sponsor's summary because median viability indices are reported. As has been stated previously, the median is an inappropriate parameter to use when evaluating a reproductive toxicology study because substantial events can go undetected; means should have been presented.

MD and HD F1 generation pups exhibited slight to moderate tremors from litter day 10 - 20. Decreased BW of HD pups probably contributed to the increased mortality described above. Incisor eruption was delayed in MD and HD pups and eye opening was delayed in HD pups. Testes descent and vaginal opening were unaffected. Locomotor coordination as assessed by the rotarod test was not impaired. F1 pups that were selected on litter day 23 for continuation in the study displayed good health for the remainder of the study. Auditory acuity and pupillary reflex in these animals were not affected by treatment. Spontaneous activity and arousal were also unaffected by treatment. Learning and memory as assessed with a watermaze was likewise unaffected by treatment. BW gain prior to pairing was unaffected as was BW gain for F during pregnancy. Fertility of the F1 generation was unimpaired.

APPEARS THIS WAY
ON ORIGINAL

III. Genetic Toxicology

A. Ames Test and WHO Nitrosation Assay (V21020) GLP, QA

Batch	F94/080A
Strains	TA98, TA100, TA1535, TA1537, WP2(pKM101), WP2uvrA(pKM101)
Concentrations	50, 150, 500, 1500, 5000 µg/plate (Ames)
Results	Results for both the plate incorporation and preincubation Ames tests were negative (i.e., < 2 fold increase in revertants), although in 1 of 2 plate incorporation experiments a statistically significant 30% increase in WP2uvrA revertants occurred at 150 - 5000 µg/plate under -S9 conditions. In the preincubation experiments, 5000 µg/ml appears to have been cytotoxic for strains TA98, TA1537, and WP2uvrA under -S9 conditions and for strain TA100 under both - and + S9 conditions because the number of revertants were notably reduced. Results for the WHO Nitrosation Assay Procedure (NAP) were positive. In the main experiment, 10 mM Naratriptan was incubated with 40 mM nitrite at 37°C at pH 2-3 and pH 3-4 (standard NAP conditions). At 1 and 4 hr, samples were removed, neutralized, and tested in the Ames plate incorporation and preincubation tests. Under -S9 conditions, both 1 and 4 hr pH 3-4 samples produced a 13 - 14 fold increase in the number of TA98 revertants, and pH 2-3 samples produced a 7.1 - 9.9 fold increase. Under +S9 conditions, 1 and 4 hr pH 3-4 samples produced a 13 - 16 fold increase in TA98 revertants and the 1 hr pH 2-3 sample produced a 3.5 fold increase. TA100 was also affected under +S9 conditions with the 1 and 4 hr pH 3-4 samples producing a 2.2 - 2.3 fold increase in revertants, and the 1 hr pH 2-3 sample producing a 2.4 fold increase. In a nitrite titration experiment using the most sensitive conditions (i.e., TA98, 4 hr incubation at pH 3-4), a concentration-dependent positive response was detected under - and +S9 conditions, even at the lowest concentration of nitrite tested, 1 mM.

B. Ames Test with Impurity-Spiked Naratriptan (V21437) GLP, QA

Batch	F716/02 spiked with 0.4% GR187174, 0.3% GR216693, and 0.2% GR54007
Strains	TA98, TA100, TA1535, TA1537, WP2(pKM101), WP2uvrA(pKM101)
Concentrations	1000, 2500, 5000 µg/plate
Results	This experiment was performed to provide additional reassurance for clinical safety because previous genotoxicity tests were conducted with batches of Naratriptan that contained lower levels of impurities than allowed by specifications. Only 3 concentrations were tested as opposed to the 5 recommended by OECD; however, this is acceptable as the study is supplementary to the complete microbial mutagenicity screen described above.

Results were negative (i.e., < 2 fold increase in revertants) in the plate incorporation test, although a statistically significant 21% increase in WP2 revertants occurred at 1000 µg/plate under -S9 conditions and similar increases in WP2uvrA revertants occurred at all concentrations under +S9 conditions.

C. Chromosomal Aberrations in Human Lymphocytes Produced by Impurity-Spiked Naratriptan (V21378) GLP, QA

Batch — C2057/47/1 and C2057/50/1 spiked with > 0.3% GR187174, 0.3% GR216693, and 0.2% GR54007

Concentrations — -S9 experiment 1: 100, **300**, 600, 800, 1000 µg/ml
-S9 experiment 2: 100, 200, **300**, 400, **500**, 600 µg/ml
+S9 experiment 1: 100, 300, 1000, 1500. 2000, 2500, **3000**, and **3354** µg/ml
+S9 experiment 2: 20000, 2500, **3000**, **3100**, 3200, 3300, 3354 µg/ml

Bolded concentrations were the only ones analyzed for chromosomal aberrations. The 3354 µg/ml is equivalent to 10 mM, the maximum noncytotoxic concentration recommended by OECD.

Results — This experiment was performed to provide additional reassurance for clinical safety because previous genotoxicity tests were conducted with batches of Naratriptan that contained lower levels of impurities than allowed by specifications. A prior experiment with human lymphocytes showed no cytogenetic damage at concentrations up to 750 µg/ml under -S9 conditions and up to 1000 µg/ml under +S9 conditions, although sufficient cytotoxicity was not achieved under +S9 conditions. In the current study, under -S9 conditions, cells were treated for the 20.5 hrs prior to harvest and under +S9 conditions, cells were treated for 3 hrs and harvested at 22.5 hrs.

In the first test under -S9 conditions, 300 µg/ml, which was associated with a relative mitotic index of 55%, produced a statistically significant increase in chromosomal aberrations excluding gaps (4% of cells v. 0.5%). However, this result did not repeat in the second test that analyzed 300 and 500 µg/ml treatments which were associated with 61 and 46% relative mitotic indices, respectively. Furthermore 4% of cells exhibiting aberrations is within the sponsor's recent historical control range.

In the first test under +S9 conditions, 3000 and 3354 µg/ml, which were associated with 76 and 50% relative mitotic indices, did not significantly increase chromosomal aberrations excluding gaps; however, 3000 µg/ml did increase aberrations including gaps, and due to cytotoxicity at 3354 µg/ml only 55 metaphases were analyzed which compromised the analysis (examination of 200 metaphases is recommended by OECD). Unspiked Naratriptan caused increases in chromosomal aberrations excluding gaps at both 3000 and 3354 µg/ml (3.5 and 5.7% of cells v. 0.5%), although only 53 metaphases were examined at 3354 µg/ml, compromising the analysis. Relative mitotic indices with 3000 and 3354 µg/ml unspiked Naratriptan were 74 and 44%, respectively. In the second test, spiked Naratriptan increased chromosomal aberrations excluding gaps at 3100 µg/ml (3% of cells v. 0.5%), but not at 3000 µg/ml and the associated relative mitotic indices were 59 and 52%. Unspiked Naratriptan did not increase aberrations excluding gaps at either 2000 or 2500 µg/ml, concentrations that resulted in relative mitotic indices of 78 and 57%, although aberrations including

gaps were increased at 2000 µg/ml. All of the increases in chromosomal aberrations under +S9 conditions fell within the range of recent historical controls (0 - 4%) except for the 5.7% of cells affected by 3354 µg/ml unspiked Naratriptan which is a compromised result because only 53 metaphases were examined.

Although this study was supplementary to a previous study using human lymphocytes, it would have been preferable for the sponsor to have analyzed 3 concentrations as recommended by OECD, particularly since adequate cytotoxicity was not achieved in the previous study under +S9 conditions. Because the increases that occurred were generally with the historical control range, Naratriptan was determined to be non-clastogenic.

D. Mutation Test (tk locus) in Mouse Lymphoma L5178Y Cells (V20298) GLP, QA

Batch C1978/270/1

Concentrations -S9 experiment 1: 500, 1000, 1500, 2000, 2500 µg/ml
-S9 experiment 2: 500, 1000, 1500, 1750, 2000 µg/ml
-S9 experiment 3: 500, 1000, 1250, 1500, 1750 µg/ml
+S9 experiment 1: 500, 1000, 1500, 1750, 2000 µg/ml
+S9 experiment 2: 500, 1000, 1250, 1500, 1750 µg/ml

Results Results were negative under both - and +S9 conditions. Concentration-dependent cytotoxicity occurred. In the first test under -S9 conditions, Naratriptan was completely cytotoxic at 2000 and 2500 µg/ml and relative survival was 10% at 1500 µg/ml, making 1500 the maximal analyzable concentration. In the second test, 1750 µg/ml was added as a concentration, but found to be too cytotoxic. In the third test, 500, 1000, 1250, and 1500 µg/ml were analyzable; relative survival was 16% at 1500 µg/ml. In the first test under +S9 conditions, Naratriptan was excessively cytotoxic at 1750 and 2000 µg/ml and relative survival was 16% at 1500 µg/ml. In the second test, 500, 1000, 1250, and 1500 were analyzable; relative survival was 17% at 1500 µg/ml.

APPEARS THIS WAY
ON ORIGINAL

IV. Carcinogenicity Studies

A. Mice, 2 yrs oral gavage (M13498) GLP, QA

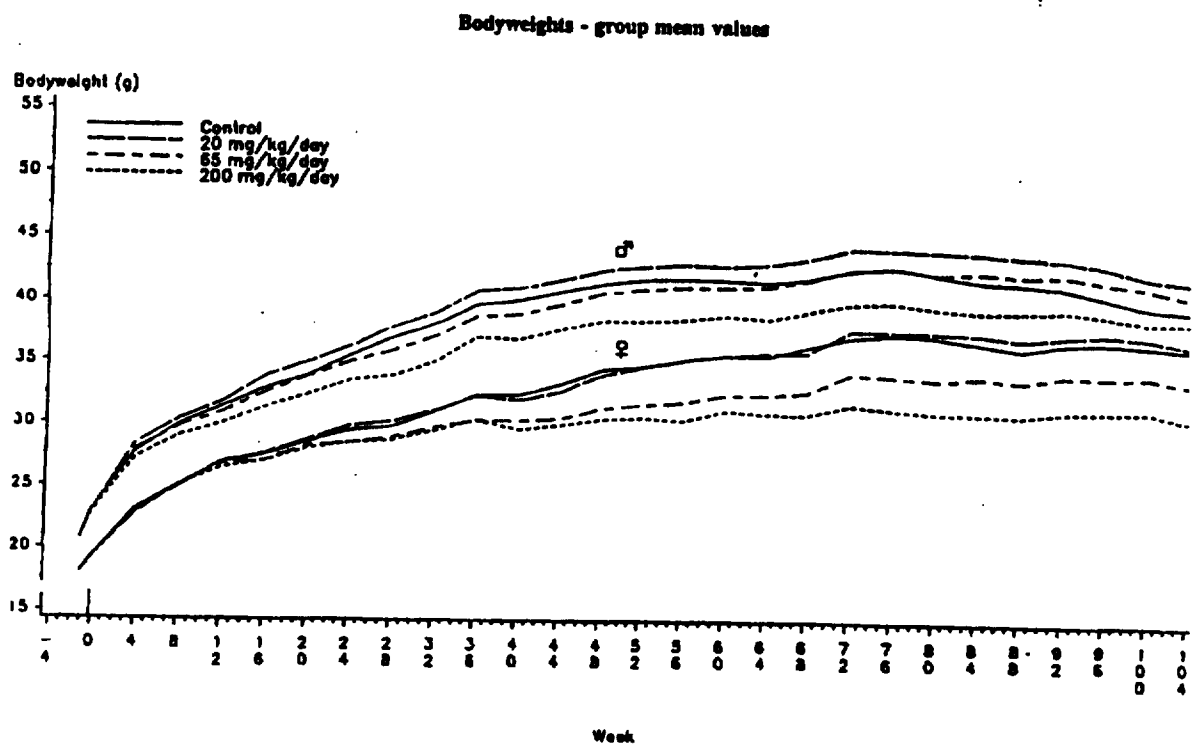
B6C3F1 mice - 20, 65, 200 mg/kg (batches F92/193A and F93/023A)
60/s/gr with 2 control groups (+ 25/s control and 60/s/gr treated for toxicokinetics)

Note: Comparisons are made to the control group with the highest incidence of any given finding.

Mortality — Survival was unaffected by treatment (80% in controls, 76% in HD).

Clinical Signs — MD and HD F showed an increased incidence of forelimb and muzzle hair loss. Two satellite HD F were lethargic on day 1 for up to 3 hrs after dosing.

Body Weight — (See sponsor-supplied figure.) BW gain was reduced throughout the study in MD and HD F, resulting in gains that were 16 and 32% less than control, respectively. These reductions in BW gain resulted in terminal BW's that were 8 and 16% less than control, respectively. BW gain was also reduced 19% in HD M during weeks 0 - 32, but was increased 7% during the same period of time in LD M. By the end of the study there was no difference in BW gain in HD M, and 14 and 7% increases were observed in LD and MD M, respectively. Food consumption was increased 5 - 7% in all treated F groups and HD M, particularly after week 12.



Hematology — There were no treatment-related changes in RBC or WBC count.

Toxicokinetics — On day 1 and at 52 and 104 weeks, blood samples from 2/s/gr were taken prior to dosing and 0.5, 1, 2, 4, 8, and 12 hr after dosing. Samples were also taken at 2 hr during weeks 12, 26, and 78. Cmax and AUC increased in a fairly dose

proportional manner and there were no consistent changes with time of measurement. Cmax and AUC tended to be higher (2 fold or less) in F than M mice. Tmax was 0.5 - 1 hr. Mean Cmax values were 710, 3710, and 6660 ng/ml and mean AUC values were 2120, 7930, and 21480 ng.h/ml, for LD, MD, and HD animals, respectively. The ratio of animal to human AUC after the maximum allowable dose (2 x 2.5 mg) was 11, 40, and 110 for LD, MD, and HD animals.

Pathology

The incidence of pituitary adenomas was increased in MD F, but there was no increase in the incidence of hyperplasia. Harderian gland adenomas were found in 13% of MD M, but the historical control range is up to 12%. Although there was an increase of Harderian gland adenomas in HD F, this incidence is within the historical control range. Tumor incidences are summarized in the table below.

Tumor Type	Incidence							
	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
pituitary adenoma[a]		3/60		2/59		**12/59**		1/60
Harderian gland adenoma	4/60	2/60	2/60	1/60	**8/60**	4/60	6/60	5/59

[a]No pituitary adenomas were reported in males in any dose group.

There were multiple non-neoplastic findings in the pituitary of MD F as indicated in the table below, with some animals exhibiting more than one pathology. Additional non-neoplastic findings included an increased incidence of ovarian abscesses in treated F and an increased incidence of tubular hyperplasia in HD F. Osteodystrophy in the nasal cavity was increased in treated F, but osteodystrophy in the femur and sternum was present in control and treated animals at similar incidences. In MD and HD F there was an increased incidence of forestomach thickening and roughening that was associated microscopically with hyperplasia and hyperkeratosis. MD F also had a higher incidence of submucosal inflammation in the stomach. The incidence of ceroid cells being found at the corticomedullary junction in the adrenal gland was higher in HD F. Related to the increased incidence of alopecia in MD and HD F, there was a dose-related increase in the number of MD and HD F with inflammatory cells in the superficial dermis. Non-neoplastic findings are summarized in the table below.

Non-neoplastic Findings	Incidence							
	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
Pituitary[a]								
enlarged		2/60		2/60		**7/60**		2/60
consequent brain depressions		2/60		0/60		**6/60**		1/60
hemorrhagic		1/60		1/60		**6/60**		1/60
raised foci		2/60		0/60		**7/60**		1/60
Ovary								
abscesses		1/60		**3/60**		**6/60**		**3/60**
tubular hyperplasia		1/59		0/60		2/60		**4/60**
Bone[b]								
osteodystrophy in nasal cavity		5/60		10/60		**22/60**		13/60
Stomach								
forestomach thickening	0/60	1/60	0/60	2/60	0/60	**8/60**	1/60	**6/60**
forestomach roughening	0/60	0/60	0/60	0/60	0/60	**9/60**	2/60	**7/60**
submucosal inflammation	2/60	3/60	1/60	0/60	0/60	**9/60**	1/60	0/60
hyperplasia/hyperkeratosis	3/60	4/60	1/60	3/60	4/60	**18/60**	7/60	**13/60**
Adrenal Glands								
ceroid cells at corticomedullary junction	1/59	11/60	0/60	14/60	0/60	18/60	0/60	**32/60**
Skin								
inflammatory cells in superficial dermis	7/60	3/60	5/60	4/60	1/60	**7/60**	2/60	**11/60**

[a]There were no findings in the pituitaries of males from any group.

[b]There was no osteodystrophy in the nasal cavity of male mice from any group.

Summary

The only neoplastic findings were an increase in pituitary adenomas in MD F and an increase in Harderian gland adenomas in MD M. The decrease in BW gain in HD F may have contributed to the lack of findings in this group; however, the increase in pituitary adenomas in MD F was not accompanied by an increase in pituitary hyperplasia. Given that final BW's for MD and HD F were 8 and 16% less than control, the study may have been better designed if the MD of 65 mg/kg had been set as the HD for F. The incidence of Harderian gland adenomas in MD M was just outside the historical control range, and the incidence in HD M was within the control range. Although exposure was >25X human exposure based on AUC, and Naratriptan is not highly metabolized in either mouse or man, it may have been advisable for the HD for males to have been set higher than 200 mg/kg given the mutagenicity of the N-nitroso metabolite of Naratriptan. The N-nitroso metabolite is formed in the stomachs of rats fed a high nitrite diet, but not rats fed a standard diet, and when Naratriptan is incubated *in vitro* in human gastric juice with a nitrite concentration that mimics conditions after a high nitrite

meal (0.3 mM), 8% is converted to the N-nitroso derivative. (Note: The concentration of Naratriptan used in the *in vitro* study was 34X the estimated stomach concentration after a 2.5 mg dose.) However, mitigating the detection of the N-nitroso metabolite is the likelihood that patients experiencing a migraine will consume little food of any kind, let alone nitrite-preserved food. It is also noted that the sponsor conducted a 13 week dose ranging study in which 400 mg/kg was determined to be too high of a dose because 4/30 mice (2 M and 2 F) died and M and F experienced a 20% decrease in BW gain.

APPEARS THIS WAY
ON ORIGINAL

B. Rats, 2 yrs oral gavage (R13500) GLP, QA

Han Wistar rats - 5, 20, 90 mg/kg (batches F93/023A and F94/080A)
55/s/gr with 2 control groups (+25/s/gr for toxicokinetics)

Notes: 1) In this study, rats were fed a nitrite supplemented diet (1000 ppm sodium nitrite) in order to assess the oncogenic potential of nitrosated drug. An N-nitroso metabolite of Naratriptan was shown to be mutagenic in the Ames test (see Genetic Toxicology section).

2) Comparisons are made to the control group with the highest incidence of any given finding.

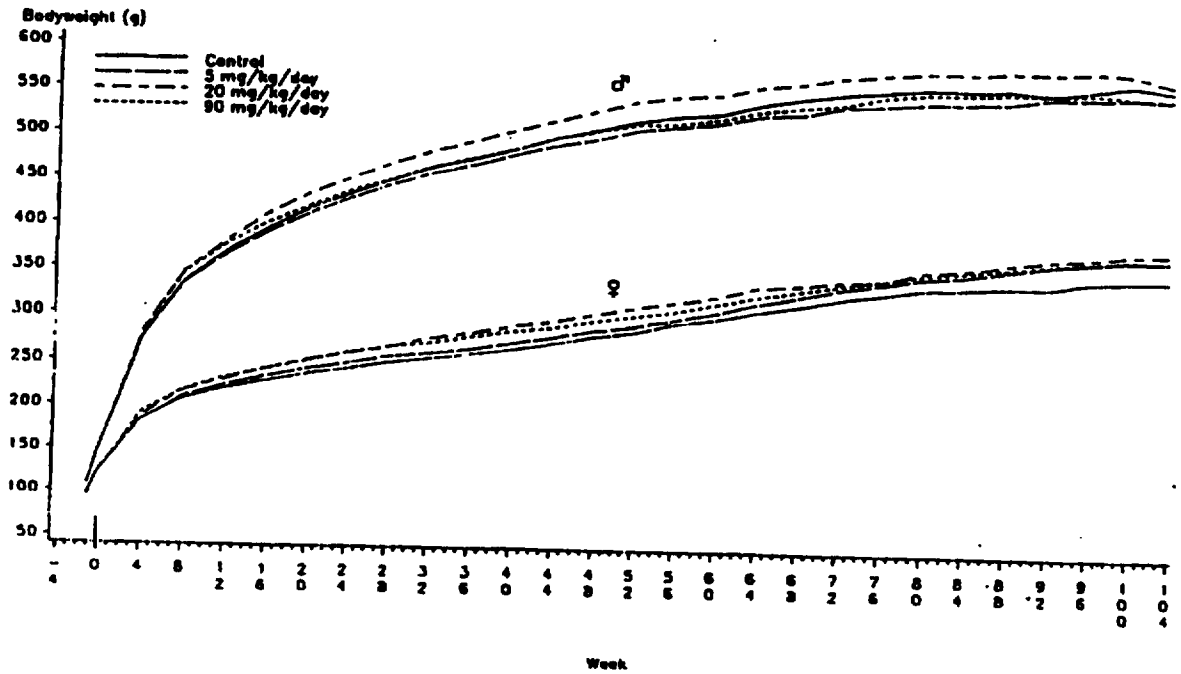
Mortality — Survival was unaffected by treatment. Survival rates were 78% in control M, 67% in control F, 75% in HD M, and 71% in HD F. It is noted that 5/16 deaths in HD F were not associated with tumors, whereas all F control deaths were ascribed to tumor development.

Clinical Signs — Salivation was observed immediately after dosing from week 3 in MD animals and from week 2 in HD animals. As of week 39 the incidence in MD animals increased from <10% to 35 - 50%, whereas HD animals experienced a higher incidence throughout the study.

Body Weight — (See sponsor-supplied figure.) BW gain was increased 9 - 13% in all treated F groups at the end of the study, resulting in BW's that were 6 - 8% greater than control. BW gain in MD and HD M was increased 4 - 5% through week 12, but there was no effect on total cumulative BW gain. Food consumption was increased 3 - 6% throughout the study in MD and HD groups.

APPEARS THIS WAY
ON ORIGINAL

Bodyweights - group mean values



Hematology There were no treatment-related changes in RBC or WBC count.

Toxicokinetics On day 1 and at 13 and 104 weeks, blood samples from 2/s/gr were taken prior to dosing and 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, and 24 hrs after dosing (except that no predose samples were taken at week 104). Samples were also taken at 2 hrs during weeks 26, 52, and 78. There were no notable gender differences and the data referred to below are from males and females combined. Tmax occurred at 0.25 - 2 hrs. Cmax increased with dose, but not always in a linear manner. AUC increased in a manner greater than predicted by linearity. Both Cmax and AUC increased over time with the rate of increase being much less between weeks 13 and 104 than during the first 13 weeks during which period AUC tended to double and Cmax increased 1.5 - 5 fold. The following table gives the ratio of animal to human AUC (2 x 2.5 mg, maximum allowable daily dose) for each dose group at day 1, week 13, and week 104.

	Ratio of Animal to Human AUC		
	Day 1	Week 13	Week 104
LD	3	7	8
MD	12	29	46
HD	101	180	309

At 52 and 104 weeks, the stomach contents of 1/s/gr were examined at 0, 5, 15, and 30 min after receiving a radiolabeled dose of Naratriptan. The nitrosated metabolite of Naratriptan was found at levels of ~2, 6, and 15 µg/ml in LD, MD, and HD groups, respectively, accounting for less than 1% of the dose. Data taken from a separate study indicates that the concentration of N-nitroso metabolite is 2X higher after a single dose than after 52 weeks of treatment.

Pathology

The incidence of benign follicular adenoma of the thyroid was increased in HD M and benign ganglioneuromas were observed in the thyroid of 2 HD F. The latter tumor type is described by the sponsor as rare in Han Wistar rats although it occurs spontaneously in Sprague-Dawley rats. The incidence of benign lymphocytic thymomas was increased in all treated F groups and the incidence of benign tubulostromal ovarian adenomas was increased in HD F, although the absolute number of tumors was low. Tumor incidences are summarized in the table below.

Tumor Type	Incidence							
	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
Thyroid								
follicular adenoma	7/55	3/55	9/55	4/55	8/54	3/55	**16/55**	1/55
benign ganglioneuroma	0/55	0/55	0/55	0/55	0/54	0/55	0/55	**2/55**
Thymus								
lymphocytic thymoma	2/51	2/54	0/54	**6/55**	0/55	4/54	1/54	**10/54**
Ovaries								
tubulostromal adenoma		1/55		1/54		1/55		**3/55**

Non-neoplastic findings in the thyroid included increased incidences of diffuse follicular hypertrophy and hyperplasia and prominent follicular cell pigmentation in HD M and F. Additionally, the incidence of cystic follicular hyperplasia increased in HD F. Increased incidences of non-neoplastic lesions in other organs were limited to localized acanthosis in LD and HD M, and uterine cystic glands in all treated F groups. Non-neoplastic findings are summarized in the table below.

Non-neoplastic Findings	Incidence							
	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
Thyroid								
diffuse follicular hypertrophy and hyperplasia	3/55	1/55	3/55	1/55	6/54	3/55	**34/55**	**8/55**
prominent follicular cell pigmentation	3/55	0/55	0/55	0/55	1/54	2/55	**35/55**	**42/55**
cystic follicular hyperplasia	10/55	4/55	4/55	3/55	8/54	3/55	10/55	**8/55**
Uterus								
cystic glands		6/55		**12/55**		**11/55**		**13/55**
Skin								
acanthosis	2/38	0/20	**6/44**	0/23	2/36	2/18	**10/39**	1/20

Summary

Thyroid follicular cell function was stimulated in both HD M and F as evidenced by hypertrophy, hyperplasia, and prominent pigmentation. Functional stimulation culminated in an increase in benign adenomas in HD M. In addition to thyroid tumors, the incidence of benign lymphocytic thymomas was increased in all treated F groups, particularly the HD group. The incidence of benign tubulostromal ovarian adenomas were also increased in HD F, although the absolute number was fairly low.

The sponsor indicates that the HD of 90 mg/kg was selected based on a preliminary 13 week study in which histopathological changes in male reproductive organs (testicular atrophy, spermatocele granuloma, etc.) occurred at doses ≥170 mg/kg. Similar pathologies were seen at 340 mg/kg in the 6 month study, and it was feared that consequent hormonal changes would confound the carcinogenicity study; therefore, the HD was set at 90 mg/kg. The specific rationale for selecting 90 mg/kg, versus any other dose less than 170 mg/kg, was not provided. While this general approach is appropriate for determining the HD for males, the HD for females could have been increased. While the HD of 90 mg/kg produces an AUC ≥100X the human AUC, dose selection based on AUC may be inappropriate given that the N-nitroso metabolite of Naratriptan is mutagenic. The N-nitroso metabolite is formed in the stomachs of rats fed a high nitrite diet (see toxicokinetics above), but not rats fed a standard diet, and when Naratriptan was incubated *in vitro* in human gastric juice with a nitrite concentration that mimics conditions after a high nitrite meal (0.3 mM), 8% was converted to the N-nitroso derivative. (Note: The concentration of Naratriptan used in the *in vitro* study was 34X the estimated stomach concentration after a 2.5 mg dose.) However, mitigating the detection of the N-nitroso metabolite is the likelihood that patients experiencing a migraine will consume little food of any kind, let alone nitrite-preserved food.

C. Rats, 2 yrs oral gavage (R13499) GLP, QA

Han Wistar rats - 5, 20, 90 mg/kg
55/s/gr with 2 control groups (+25/s/gr for toxicokinetics)

(batches F93/023A and F94/080A)

Notes: 1) This study was essentially the same as study 13500 described above, except that rats were fed a standard diet that was not enriched in nitrite.

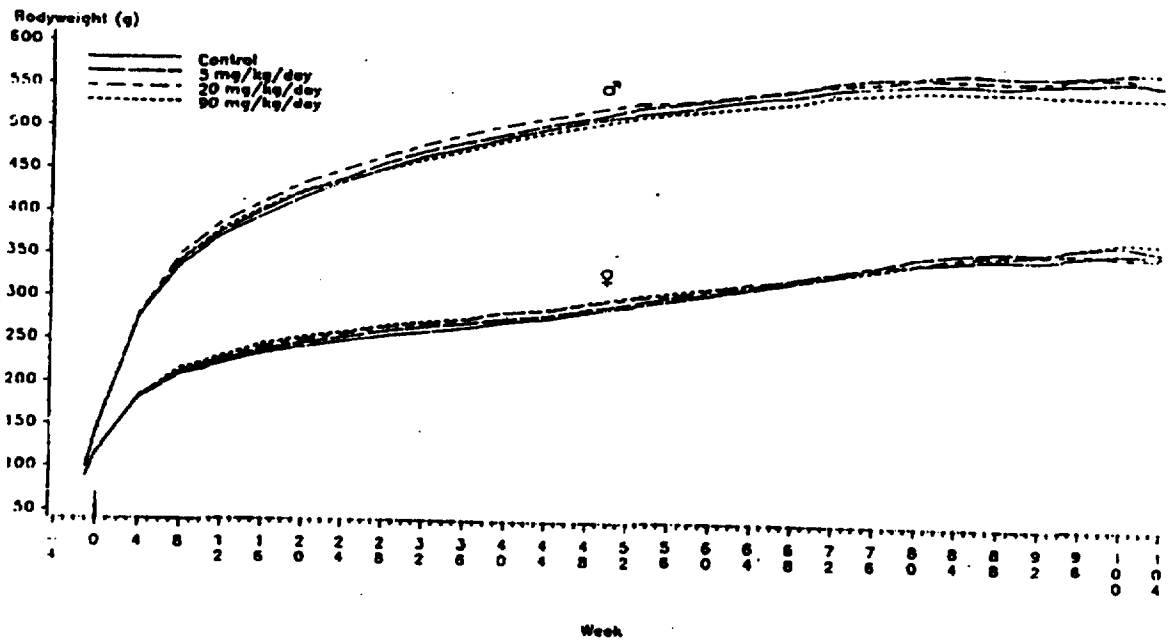
2) Comparisons are made to the control group with the highest incidence of any given finding.

Mortality — Survival was not adversely affected by treatment. Survival rates were 78% for control and HD M, 67% for control F, and 80% for HD F.

Clinical Signs — Salivation was observed immediately after dosing from week 2 in MD animals (<10% incidence) and from week 1 in HD animals (up to 63% incidence). The incidence of hair loss and the number of sites affected were increased in HD animals.

Body Weight — (See sponsor-supplied figure.) BW gain over the entire 104 weeks was not affected by treatment; however, in the first 12 weeks, BW gain by MD and HD groups was 5 - 10% greater than control. After this initial period BW gain by HD M was 7% less than control, and BW gain by other groups was similar to control. Food consumption throughout the study was 5 - 8% greater in MD and HD M than controls.

Bodyweights - group mean values, Main group rats



Hematology — There were no treatment-related changes in RBC or WBC count.

Toxicokinetics

On day 1 and at 13 and 104 weeks, blood samples from 2/s/gr were taken prior to dosing and 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, and 24 hrs after dosing (except that no predose samples were taken at week 104). Samples were also taken at 2 hrs during weeks 26, 52, and 78. There were no notable gender differences and the data referred to below are from males and females combined. Tmax occurred at 0.25 - 4 hrs, generally at 0.25 - 2 hrs. AUC and Cmax increased with dose, but not always in a linear manner. Cmax increased 1.3 - 6.0X between day 1 and week 13, and then tended to stabilize. Generally AUC increased over time with the rate of increase being much less between weeks 13 and 104 than during the first 13 weeks during which period AUC tended to double. The following table gives the ratio of animal to human AUC (2 x 2.5 mg, maximum allowable daily dose) for each dose group at day 1, week 13, and week 104.

	Ratio of Animal to Human AUC		
	Day 1	Week 13	Week 104
LD	5	7	11
MD	18	40	82
HD	113	236	218

At 52 and 104 weeks, the stomach contents of 1/s/gr were examined at 0, 5, 15, and 30 min after receiving a radiolabeled dose of Naratriptan. The nitrosated metabolite of Naratriptan was not detected.

Pathology

The incidence of benign follicular adenoma of the thyroid was increased in HD M and the incidence of benign c-cell adenoma was increased in both HD M and F. The incidence of benign testicular interstitial cell adenoma was increased in HD M, but the absolute number of tumors was low. Tumor incidences are summarized in the table below.

Tumor Type	Incidence							
	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
Thyroid								
follicular adenoma	6/55	5/55	2/55	2/55	4/55	4/55	**15/55**	2/55
c-cell adenoma	4/55	5/55	5/55	6/55	7/55	4/55	**10/55**	**11/55**
Testes								
interstitial cell adenoma	1/54		2/55		2/55		**3/55**	

Non-neoplastic changes in the thyroid of HD animals included increased incidences of diffuse follicular hypertrophy/hyperplasia, focal cystic follicular hyperplasia, and prominent follicular cell pigmentation. Other organs in which there was an increased incidence of hyperplasia included the testes, thymus, and pituitary. Localized or irregular vacuolation of the cerebral cortex was observed in 2 HD M; however, in the companion study 13500, focal vacuolation is described in 1 Control and 1 LD M, although the area of the brain affected is not stated. Focal ependymal vacuolation was observed in 1 HD F.

There were a few changes in the urogenital tracts of HD M probably reflective of the slightly higher incidence of urinary tract infections in this group. Related to the increased hair loss observed in HD animals, atrophy of hair follicles was more common in HD M as was epithelial hyperplasia in the tail. Other findings that occurred in small numbers or had small incidence increases included focal epicardial thickening in 2 HD M and 1 HD F, an increased incidence and severity of biliary proliferation in all treated M groups, an increased incidence of acinar hyperplastic foci in the pancreas of HD M, an increased incidence of prostatitis in HD M, and an increased incidence of sternum chondropathy in HD F. The non-neoplastic findings described above are summarized in the table below.

Non-neoplastic Findings	Incidence							
	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
Thyroid								
diffuse follicular hypertrophy and hyperplasia	4/55	0/55	0/55	0/55	0/54	0/55	**12/55**	1/55
prominent follicular cell pigmentation	4/55	1/55	0/55	0/55	0/54	0/55	**47/55**	**42/55**
cystic follicular hyperplasia	5/55	3/55	10/55	3/55	7/54	2/55	**15/55**	**8/55**
Testes								
interstitial cell hyperplasia	1/55		**5/55**		**4/55**		**4/55**	
seminal vesiculitis	5/55		6/55		3/55		**9/55**	
Thymus								
focal epithelial hyperplasia	4/49	18/54	5/51	15/53	7/53	18/54	**8/52**	**27/54**
Pituitary								
focal hyperplasia	8/55	14/55	**13/55**	14/55	10/54	16/55	**14/55**	16/55
Brain								
localized vacuolation of ctx	0/55	0/55	0/55	0/55	0/55	0/55	**1/55**	0/55
irregular vacuolation of ctx	0/55	0/55	0/55	0/55	0/55	0/55	**1/55**	0/55
focal ependymal vacuolation	0/55	0/55	0/55	0/55	0/55	0/55	0/55	**1/55**
Kidney								
pelvic epithelial hyperplasia	4/55	12/55	6/55	10/55	4/55	7/55	**9/55**	8/55
Urinary Bladder								
reddened	1/55	1/55	2/55	0/55	1/55	1/55	**5/55**	0/55
thickened	1/55	1/55	1/55	0/55	0/55	1/55	**3/55**	0/55
calculi present	1/55	1/55	2/55	0/55	0/55	0/55	**4/55**	0/55
Skin								
hair follicle atrophy	17/53	37/54	18/50	34/55	**27/49**	34/54	**27/51**	43/54
epithelial hyperplasia (tail)	3/16	3/9	3/16	3/12	6/27	4/11	**12/25**	1/10
Heart								
focal epicardial thickening	0/55	0/55	0/55	0/55	0/55	0/55	**2/55**	**1/55**
Liver								
biliary proliferation	6/55	24/55	**11/55**	20/55	**11/55**	9/55	**10/55**	20/55
Pancreas								
acinar hyperplastic foci	1/54	0/54	1/55	0/55	0/55	0/55	**4/55**	0/55
Prostate								
prostatitis	9/55		6/55		8/55		**18/55**	
Bone								
chondropathy (sternum)	5/55	6/53	6/55	11/55	5/55	7/55	8/55	**15/55**

Summary

Thyroid follicular cell function was stimulated by Naratriptan as evidenced by hyperplasia in all treated male groups and HD F, and prominent cellular pigmentation in HD M and F. Functional stimulation culminated in an increase in benign follicular adenomas in HD M. The incidence of benign c-cell adenomas was increased in HD M and F. In addition to the changes that occurred in the thyroid, increased incidences of hyperplasia occurred in testes, thymus, pituitary, pancreas, and pelvic epithelium of the kidney of HD M and/or F. In the testes, the incidence of benign interstitial cell adenomas was increased in HD M, although the absolute number was low.

The sponsor indicates that the HD of 90 mg/kg was selected based on a preliminary 13 week study in which histopathological changes in male reproductive organs occurred at a dose level of 170 mg/kg. In order to avoid confounding hormonal imbalances consequent to testicular effects, the HD for the carcinogenicity study was set at 90 mg/kg; the rationale behind specifically selecting 90 mg/kg, versus any other dose less than 170 mg/kg, was not provided. While this general approach is appropriate for determining the HD for males, the HD for females could have been increased. While the HD of 90 mg/kg produces an AUC ≥100X the human AUC, dose selection based on AUC may be inappropriate given that the N-nitroso metabolite of Naratriptan is mutagenic. The N-nitroso metabolite is formed in the stomachs of rats fed a high nitrite diet (see study 13500 reviewed above), but not rats fed a standard diet, and when Naratriptan was incubated *in vitro* in human gastric juice with a nitrite concentration that mimics conditions after a high nitrite meal (0.3 mM), 8% was converted to the N-nitroso derivative. (Note: The concentration of Naratriptan used in the *in vitro* study was 34X the estimated stomach concentration after a 2.5 mg dose.) However, mitigating the detection of the N-nitroso metabolite is the likelihood that patients experiencing a migraine will consume little food of any kind, let alone nitrite-preserved food.

SUMMARY AND EVALUATION

Background

Neuronal and vascular mechanisms are believed to work in concert in the development of migraines. It is theorized that activation of the trigeminal nerve results in release of inflammatory mediators into the adventitia of intracranial blood vessels. Subsequent dilation and edema underlie the pain experienced during a migraine. Anticipation that vasoconstriction could alleviate migraine symptoms has led to the development of 5HT agonists for this purpose. Agonists for the 5HT1 receptor subtype are selective for cranial blood vessels over coronary vessels, theoretically allowing constriction of cranial vessels without complicating coronary vasospasms. Specifically, $5HT_{1B/1D}$ agonists are being developed for the treatment of migraine. Naratriptan is one such agonist and is structurally related to Sumatriptan which is marketed for the treatment of migraine. Potential advantages of Naratriptan over Sumatriptan include increased bioavailability (60%) and an increased half life ($t_{1/2}$ = 5 hrs) that may decrease the incidence of headache recurrence.

Pharmacology

Naratriptan binds to cloned $5HT_{1D}$, $_{1D\alpha}$, and $_{1D\beta}$ receptors with K_i's of 8, 13, and 13 nM, respectively. While Naratriptan's affinity for these receptors is 3 - 6 times greater than Sumatriptan's, Naratriptan's specificity is less, because Naratriptan's affinity for $5HT_{1A}$ is 13 times greater than Sumatriptan's (K_i = 79 nM). Thus, generalized effects on systems other than cranial blood vessels may be more likely with Naratriptan; however, this does not necessarily translate into an increased risk for coronary complications because evidence indicates that the $5HT_2$ receptor is the subtype present in coronary arteries (Lai *et al.*, 1991). Naratriptan has little effect at $5HT_2$ receptors *in vitro*, causing no contraction of rabbit aorta, rat tail artery, or dog femoral artery. In a general receptor binding screen, Naratriptan did not demonstrate striking affinity for any non-serotonergic receptor tested

Naratriptan was ~3 times more potent than Sumatriptan in causing constriction of basilar and middle cerebral arteries isolated from dog. (In the IND

) In anesthetized dogs, Naratriptan increased carotid arterial resistance with an ED50 of 19 µg/kg intravenously and 190 µg/kg intraduodenally. Intravenously administered Naratriptan also increased the vascular resistance in femoral and vertebral artery beds and produced a transient response in the renal artery, but effects were less than in the carotid bed. These effects were also seen with Sumatriptan, although Naratriptan was more potent. Naratriptan also produced increases (≤30%) in coronary artery resistance that were not observed with Sumatriptan, suggesting that the potential for coronary vasospasm may be greater with Naratriptan than Sumatriptan. The effect on the coronary vascular may be secondary to bradycardia, because pretreatment with propranolol blocked the vascular effect. When the effect of Naratriptan on isolated human and monkey coronary arteries was tested, the extent of contraction was similar to that produced by Sumatriptan, but Naratriptan's potency was 4 - 8 times greater, again suggesting that the potential for coronary vasospasm may be greater with Naratriptan than Sumatriptan.

Safety pharmacology studies revealed long-lasting tachycardia (up to a 79% increase in HR for ≥5 hrs) in dogs after oral administration of 1 and 3 mg/kg. Pharmacokinetic data from toxicology studies indicate that the 1 mg/kg dose results in an AUC 6 times greater than the AUC achieved in patients after the maxiumum allowable daily dose of 2 x 2.5 mg. When 10, 100, and 1000 µg/kg Naratriptan were administered intravenously to an anesthetized cat, diastolic and systolic blood pressure were transiently increased; increases of ~50% were observed at 100 and

1000 μg/kg. This effect on blood pressure was not seen in the monkey. Naratriptan was demonstrated to have no effect on pentobarbitone sleep time and to undergo no metabolism by MAO (there was no increase in carotid vasoconstriction in dogs treated with the MAO inhibitor, pargyline).

Absorption, Distribution, Metabolism, and Excretion (ADME)

ADME studies revealed Naratriptan to be well absorbed; bioavailability was 100, 70 - 100, and 60% in rats, dogs, and humans, respectively (bioavailability in the rat is a guesstimate based on i.v. and oral data from different strains). Exposure generally increased linearly with dose in the animal species tested. Tmax ranged from 0.5 - 6 hrs and $t_{1/2}$ from 2 - 9 hrs. There was some evidence of accumulation in rats as AUC values were increased (generally <2 times) between days 1 and 24 or 99, but no further increase in AUC occurred between days 99 and 190, and there was no evidence of accumulation in dogs. Naratriptan distributed rapidly to most tissues with peak levels detected at 1 hour in rats. Whereas the concentration declined in most tissues by 6 hours, levels in the gonads and eye did not, with highest levels in the gonads achieved at 24 hrs, and 60% of the 1 hour level remaining in the eye at 1 week. It is noteworthy that these two organs were affected in toxicology studies. Plasma protein binding was low in all species including man, ranging from 25 - 35%. After oral dosing in most species, parent drug accounts for the majority of drug in plasma, with the N-oxide also being present in dog and the N-oxide and piperidone also being present in humans. Naratriptan accounts for the majority of drug in the urine as well, although a number of metabolites are also present. Naratriptan is nitrosated in the stomachs of rats fed a high nitrite diet and *in vitro* in human gastric juice under conditions that mimic a high nitrite meal (note that the concentration of Naratriptan used *in vitro* was 34 times what is predicted to be in the human stomach after a 2.5 mg dose). Although the N-nitroso metabolite was found to be mutagenic in the Ames test, there were no major findings in the toxicology or oncogenicity studies that were unique to the rats fed a high nitrite diet (see below). Naratriptan is excreted in urine (rat ~35%, dog ~70%) and feces (rat ~55%, dog ~30%), primarily as parent drug. In rats there is little biliary excretion and renal clearance exceeds GFR, suggesting active secretion.

General Toxicity

Acute studies were conducted in mice and rats. The maximum nonlethal oral dose was 1000 mg/kg in mice and 750 mg/kg in rats, doses that are 1000 and 1500 times the maximum daily human dose (2 x 2.5 mg) on a mg/m^2 basis. These doses were associated with tremors, unsteady gait, subdued behavior, prostration, and low posture on day 1 and decreased BW between days 1 and 3 in mice. Similar observations were made in rats, two of which died within 24 hours of receiving a 1000 mg/kg dose. Three other rats given 1000 mg/kg, one of which convulsed, were killed for humane reasons. Testes and epididymides weights were increased and pathology noted on days 2, 3, and 15 included dilation of seminiferous tubules, sperm depletion, sperm granulomas, and interstitial edema. The NOEL for testicular/epididymal effects was 170 mg/kg, 330 times the maximum recommended daily human dose on a mg/m^2 basis.

Subchronic oral studies were conducted in rats and dogs. One month and six month studies were conducted in rats, and 44 day and 1 year studies were conducted in dogs. From day 8 onward in the 1 month rat study, which used doses of 10, 40, 170, and 340 mg/kg, BW was less than control in HD males and food consumption was decreased in 170 and 340 mg/kg males and females. Water intake and urine volume were increased ~40% and urinary chloride was increased ~50% in HD animals. RBC's were decreased 4% relative to control in HD F and reticulocytes were increased 12 and 29% relative to control in HD males and females, respectively. There were no changes in either parameter after a 1 month recovery period. There were dose-dependent decreases relative to control in serum protein in both sexes (6% at the HD) and albumin in females (6% at the HD), suggesting possible effects on the kidney, but effects resolved during recovery. Glucose was slightly increased in 170 and 340 mg/kg males and cholesterol was slightly decreased

in HD animals, but not after the recovery period. Relative liver weight was minorly increased in HD females, but this increase was not apparent after the recovery period. Liver necrosis was observed in 4/27 HD animals as opposed to 1/25 controls, infarction and periportal fibrosis were observed in 1 HD female, and hemorrhage was observed in another HD female. Liver histopathology was not examined after recovery. Testicular atrophy associated with epididymal atrophy and spermatozoal depletion occurred in 6/13 HD males, but the incidence of testicular atrophy was within control limits after the recovery period. The NOEL for the testicular effects was 170 mg/kg which is associated with an AUC that is 230 times greater than occurs in humans after the maximum recommended daily dose of 2 x 2.5 mg. The overall NOEL for this study was 40 mg/kg which was associated with an AUC 44 times greater than occurs in humans after the maximum recommended daily dose.

In the six month rat study, doses of 10, 60, and 340 mg/kg were used and there were two groups each of controls and HD animals, one was fed a standard diet and the other was fed a high nitrite diet in order to promote formation of the potentially toxic N-nitroso metabolite in the gastrointestinal tract (see nitrosation information in the ADME section above). In general, the toxicity profile was not dramatically different in nitrite-fed animals; a few specific differences are enumerated below. Mortality attributed to treatment in the HD groups was 12/32 (-nitrite) and 7/32 (+nitrite), with most deaths occurring between days 70 - 110. No cause of death was established. Clinical signs at the MD and HD included salivation, vocalization, and aggression. As in the 1 month study, BW gain was decreased in HD males; however, food consumption was increased in males and females. As in the 1 month study, water intake and urine volume were increased in HD animals. Hematological changes included 2 - 10% increases in Hb concentration, MGH, hematocrit, MCV, and thrombotest clot time in HD males; however, HD males fed a high nitrite diet did not have increases in Hb concentration or hematocrit, which may reflect an effect of the nitrite diet because nitrite fed controls had decreased Hb concentration and hematocrit. Some of the above hematological changes were also observed in MD males. As in the 1 month study, RBC's were decreased 3 - 6% in HD animals (males and females in this study) and reticulocytes were increased 11- 21% relative to control, although one increase in reticulocytes was observed at a time point when RBC's were not decreased and vice versa. Hematological changes generally resolved during recovery. As in the 1 month study, HD animals had decreased serum protein and albumin levels relative to controls, although most changes occurred only in nitrite-fed animals in this study. Minor decreases in cholesterol (HD males), triglycerides (HD males), and glucose (MD and HD males and females) may suggest changes in liver function, but unlike in the 1 month study, there were no notable histopathological findings in the liver. There were no noteworthy changes in organ weights, but there was a reduction in size of the testes and epididymides in HD males that was associated with atrophy of seminiferous tubules, spermiostasis, tubular mineralization, interstitial inflammation, sperm granulomas, and diffuse interstitial hyperplasia. Seminiferous and epididymal atrophy did not revert during recovery. Because testicular and epididymal weight increases and seminiferous tubule dilation were noted in acute studies, the sponsor suggests that drug treatment acutely increases seminiferous tubule fluid and with repeated exposure the resulting increase in pressure results in atrophy. Lesions in female reproductive organs included an increased incidence of ovarian atrophy, follicular/luteal cysts, and anestrus in HD females. While ovarian atrophy was not observed after the recovery period, cysts and anestrus persisted. Histopathological effects in organs other than reproductive organs were limited to reversible atrophy of granular ducts in salivary glands of HD animals that may have been secondary to the effects on reproductive organs because the sponsor states that salivary glands are sensitive to sex steroids. The NOEL for histopathological changes was 60 mg/kg, which is associated with an AUC that is 85 times greater than occurs in humans after the maximum recommended daily dose of 2 x 2.5 mg. The overall NOEL (due to hematological changes at 60 mg/kg) was 10 mg/kg which is associated with an AUC that is 8 times greater than occurs in humans after the maximum recommended daily dose.

In the 44 day dog study, dogs were given 1.0, 2.25, and 5.0 mg/kg. BW was not affected by treatment. Clinical signs included pupil dilation, corneal stippling, and occasional difficulty in waking in all groups, and hindlimb stiffness that increased in incidence with dose, but stopped occurring after day 14. The changes in the precorneal tear film described as corneal stippling were not corneal opacities, according to the sponsor. Stippling was transient, disappearing by 24 hours after dosing, and occurred only during the first 2 - 3 weeks of treatment. Cardiovascular changes included a 25 - 31% increase in heart rate in MD and HD males, and an 11% decrease in QT interval (ventricular contraction time) in HD males. Tachycardia was also seen in the dog safety pharmacology described above. Although no effects were reported in the six month dog study described below, recordings in that study were made prior to dosing when the plasma concentration of drug was negligible. Hematology changes included 7 - 9% decreases in RBC's and hematocrit in MD and HD females and an increase in reticulocytes in HD males (but at week 3 and 6, only 1/5 HD males had values outside the control range (≤27%)). In contrast to what was observed in rats, plasma protein was increased 6 - 9% in MD and HD males with a transient increase in α1-globulin and decrease in albumin/globulin ratio in HD males. Also in contrast to the minor decreases in cholesterol seen in rats, a minor increase in cholesterol occurred in HD male dogs. Histopathological findings included slight mononuclear infiltration around several meningeal and cerebral vessels in 1/3 HD males, described as an unusual finding in the beagle, corneal ulceration in 1/3 MD males, and various testicular changes including tubular atrophy in one MD male, diffuse tubular degeneration in one LD male, and sperm aggregates in the seminiferous tubules of one LD and two HD males. There were no NOEL's for the testicular histopathology or corneal stippling. The NOEL for tachycardia in this study was 1.0 mg/kg which was associated with an AUC that was 6 times greater than occurs in humans after the maximum recommended daily dose of 2 x 2.5 mg; however, tachycardia was observed after a 1 mg/kg dose in the safety pharmacology study. The NOEL for minor hematology changes was also 1.0 mg/kg. Although the mononuclear cell infiltration into meninges and cerebral vessels that occurred at 25 times the human AUC was described as an unusual finding in the beagle, it may be explained by reports that serotonin activates monocytes by acting on the muramyl peptide receptor.

Doses used in the one year dog study were the same as for the 44 day study, 1.0, 2.25, and 5.0 mg/kg. Two HD males were killed for humane reasons after experiencing repeated convulsive episodes nine months into the study. Other clinical signs were those seen in the 44 day study, pupil dilation, difficulty in waking, and hindlimb stiffness and corneal stippling that were limited to the first two weeks of treatment. Salivation was reported in this study, but not in the 44 day study. Although there were no ECG changes at 3, 6, 9, or 12 months, this likely reflects that recordings were made prior to dosing when plasma levels of Naratriptan were negligible. Although Hb, hematocrit, and RBC's were decreased 4 - 14% in MD and HD animals, changes generally reversed by 9 months. Clinical chemistry changes included 60 - 80% increases in AP in some HD females and an 8-fold increase in ALT in the HD male that severely deteriorated after experiencing multiple convulsions. The dog that severely deteriorated exhibited agonal hemorrhage and focal mucosal necrosis in the stomach, but there were no findings that fully explained the poor clinical condition of this and one other HD male. Other histopathological changes were limited to the thyroid; at the six month interim one HD male displayed moderate hypertrophy of the thyroid follicular epithelium, and at the end of the study one LD female had developed thyroid follicular cell adenoma. As in the 44 day study, there was no NOEL for corneal stippling or other clinical signs such as pupil dilation and hindlimb stiffness. Minor hematological changes had a NOEL of 1.0 mg/kg which was associated with an AUC that was 6 times greater than the AUC obtained in humans after the maximum recommended daily dose of 2 x 2.5 mg. The NOEL for convulsion and deterioration was 2.25 mg/kg which was associated with an AUC that was 13 times greater than the AUC obtained in humans after the maximum recommended daily dose.

The corneal stippling that occurred in both dog studies was pursued in several acute investigational studies. Fluorescein staining demonstrated that no epithelial damage to the cornea occurred, even at the time of maximum tear film reaction. Topical application of saline ameliorated the reaction as did intravenous administration of a 5HT1 antagonist. The mechanism by which stippling occurs is unknown, but the mechanism is not distribution of Naratriptan into the eye because topical application of Naratriptan to the eye did not produce stippling. Distribution of a metabolite into the eye, however, remains a possibility.

In summary, the following toxicological findings were observed in multiple studies and/or across species. Tachycardia was observed in the safety pharmacology and the 44 day dog study and was accompanied by a small decrease in QT interval in the latter study. The LOEL's for these studies were 1 and 2.25 mg/kg, respectively. Although tachycardia was not reported in the one year dog study, this reflects that recordings were made prior to dosing when plasma levels of Naratriptan were negligible. Testicular and epididymal histopathological changes occurred in the acute, the 1 month, and the 6 month rat studies, with a LOEL of 340 mg/kg, and seminiferous and epididymal atrophy did not revert during a 1 month recovery. There were various testicular findings in the 44 day dog study, but unlike in rats, atrophy was not a consistent attribute and no testicular findings were reported in the 1 year dog study. In all subchronic and chronic rat and dog studies, there were minor decreases in RBC's that were sometimes accompanied by increases in reticulocytes. Lastly, corneal stippling was observed in all dog studies, even after a single dose. The mechanism and clinical significance of this finding is unclear, but it is noted that stippling ceased occurring after 2 - 3 weeks of treatment.

Reproductive Toxicity

Reproductive toxicology studies were conducted in rats and rabbits. A combined Segment I, II, III study in rats (10, 60, 170, 340 mg/kg p.o.) revealed a reduction in testes and epididymis size in F0 males given 340 mg/kg that was accompanied by seminiferous tubular atrophy, epididymal atrophy and granuloma, and depletion of spermatozoa. Some affected males failed to mate successfully. F0 females given 340 mg/kg experienced a 30% decrease in BW gain during pregnancy. The proportion of females with normal estrous cycles was decreased in a dose-dependent manner, with only 36% of animals given 340 mg/kg displaying normal estrous cycles. Examination of uterine contents revealed increased preimplantation loss at doses of 60, 170 and 340 mg/kg. In the 340 mg/kg group, losses culminated in a 47% decrease in the number of live fetuses per dam and a 34% decrease in the number of live births per litter from dams that were allowed to litter. In an effort to further investigate the observed preimplantation loss, treated males from the initial study were mated with untreated females. As in the primary study, insufficient numbers of animals were used, 11 - 12 per group, and only 8 pregnancies resulted in the 340 mg/kg group. In this study, preimplantation loss was again increased in the 340 mg/kg group, primarily due to 2/8 animals that had losses in excess of 85%. In an additional investigational Segment I study, when untreated males were mated with female rats dosed 22 days prior to mating through GD12, evidence again suggests that preimplantation loss was increased in the 170 and 340 mg/kg groups. This information was overlooked by the sponsor partly because preimplantation loss was calculated as total number of losses per group/total number of lutea per group rather than loss/litter, and partly because one animal from each of these groups was sacrificed on day 38 of treatment because there was no evidence of mating, and these animals were not included in the sponsor's analysis. Post-mortem examination showed both animals to be pregnant and to have sustained significant preimplantation losses. When these animals are included in the analysis, whereas the highest control preimplantation loss was 12.5%, 2/8 animals receiving 170 mg/kg sustained losses of 29 and 62%, and 2/9 animals receiving 340 mg/kg sustained losses of 29 and 44%. It is noted, that again in this study insufficient numbers of animals were examined. Based on the studies described above, it has not been definitively established whether preimplantation loss is affected through the female, the male, or both. In comparison to the exposure obtained in

humans after the maximum recommended dose of two 2.5 mg tablets/day, AUC's achieved in nonpregnant rats given 10 (NOEL), 60, 170, and 340 mg/kg were 11, 70, 240, and 470 times, respectively, greater than AUC's achieved in humans. AUC data from pregnant rats is not available, but plasma levels taken 1 hour after dosing were similar in pregnant and nonpregnant animals.

When fetuses were examined in the combination Segment I, II, III study, no major treatment-related abnormalities were noted, but skeletal defects indicative of fetal development delay were noted at 60, 170, and 340 mg/kg. In the Segment III portion of the study, of the 8 HD litters that were delivered (which is an inadequate number), 1 was eaten by day 2, and 2 others died by day 4, leaving only 5 litters for evaluation. As previously indicated, there was a 34% decrease in the number of live births per litter born to dams given 340 mg/kg. Physical development and locomotor coordination of F1 animals that survived was unimpaired. Due to the limited number of 340 mg/kg litters, animals were not selected from this group for further study. Selected individuals from the other dosage groups showed no impairment of hearing, pupillary reflexes, or learning and memory as assessed with a watermaze. When selected F1 individuals were mated, there was no evidence of compromised fertility. The F2 generation was not hindered in terms of physical development or locomotor coordination, and no there were no notable post mortem findings.

In a separate rat Segment II study (10, 60, 340 mg/kg p.o.), Naratriptan was again shown not to be teratogenic even at 340 mg/kg which reduced maternal BW gain. As in the previously described study, delays in skeletal ossification were observed in the 60 and 340 mg/kg groups. Post-implantation loss was increased at 340 mg/kg, but only 1 litter experienced losses greatly beyond the control range. The NOEL of 10 mg/kg provides a safety margin of 11 when AUC's achieved in non-pregnant rats are compared to the AUC associated with two 2.5 mg tablets (the maximum recommended dosage) given to patients. It is difficult to make a comparison based on Cmax because the Cmax achieved in humans when taking a second 2.5 mg tablet 4 hrs after the first 2.5 mg tablet has not been established. If comparisons are simply made to the Cmax achieved in humans after a single dose, the safety factor is 28.

Two Segment II studies using doses of 1, 5, and 30 mg/kg p.o. were conducted in rabbits, one in Dutch rabbits, the other in New Zealand white rabbits. In Dutch rabbits, but not New Zealand rabbits, post-implantation loss was increased at all doses, being 28, 25, and 22% for LD, MD, and HD groups versus 14% for controls (historical control range is 3 - 15%). The sponsor reports an increase only at the MD and HD because the sponsor inappropriately calculated mean loss as total losses per group/total implantations per group, rather than averaging the loss per litter. Maternal toxicity, as evidenced by BW loss, occurred in Dutch rabbits only at 30 mg/kg. In the Dutch rabbit study, minimal fetal vascular and skeletal variations occurred. Vascular variations included increased incidences of abnormal common carotid arteries (14% in HD v. 9% in control), abnormal origin of cervical trunks (10, 10, 7% in LD, MD, HD v. 4% in control), and accessory cervical trunks (14, 12, 14% in LD, MD, HD v. 7% in control). The first two findings were outside the historical control range, whereas the latter finding was within the historical control range. Skeletal variations included an increased incidence of supernumerary ribs (10, 19, 14% in LD, MD, HD v. 4% in control) and incomplete ossification of forepaw phalanges (22, 35, 19% in LD, MD, HD v. 16% in control). Plasma levels were taken 1 hour after dosing, which had previously been shown to be the Tmax in Dutch rabbits, and were 8, 78, and 420 times the Cmax achieved in humans with a single 2.5 mg dose. No AUC data was provided. In the New Zealand rabbit study, fetal weight gain was decreased 8 - 9% at all doses. Unlike with Dutch rabbits, there were no effects on cervico-thoracic vasculature. Skeletal variations in MD and HD fetuses included an increased incidence of 6 lumbar vertebrae, 13 thoracic vertebrae, and 13 ribs. There was also an increased incidence of the 6th sternebra not being ossified, but all of these changes fell

within the historical control range. There was an increased incidence of incomplete ossification of phalanges at all doses (24, 17, 24% in LD, MD, HD v. 12% in control) for which no historical control data was provided. Reduced BW gain by MD and HD dams probably contributed to the retarded development of fetuses. AUC's achieved in LD, MD, and HD rabbits were 2.5, 19, and 140 times, respectively, the AUC associated with two 2.5 mg tablets given to patients. Cmax values were similar to the 1 hr plasma levels reported in Dutch rabbits.

In a rat Segment III study (10, 60, 340 mg/kg p.o.), the incidence of litters with stillborn pups was increased in the HD group (6/15 v. 1/15 controls), with 1 litter having 10/11 pups stillborn. Pup deaths occurred in the majority of HD litters prior to day 4, with four litters being lost entirely; two MD litters lost five pups each prior to day 4. Consequently, only 11 HD litters could be evaluated for effects on the F1 generation. MD and HD F1 animals exhibited slight to moderate tremors from litter day 10 - 20. Decreased BW gain of HD pups probably contributed to the increased mortality described above; similar results were obtained in the Segment III section of the combined study described above. Incisor eruption was delayed in MD and HD pups and eye opening was delayed in HD pups. Testes descent and vaginal opening were unaffected. Locomotor coordination as assessed by the rotarod test was not impaired. F1 pups that were selected on litter day 23 for continuation in the study displayed good health for the remainder of the study. Auditory acuity, pupillary reflex, spontaneous activity, and learning and memory were not affected in these animals. BW gain prior to pairing was unaffected as was BW gain for females during pregnancy. Fertility of the F1 generation was unimpaired.

Genotoxicity

Naratriptan was evaluated for genotoxicity using the Ames test, mutation test in mouse lymphoma cells, chromosomal aberration test in human lymphocytes, and *in vivo* micronuclei test in mice. Although Naratriptan itself was nongenotoxic, when tested in the WHO Nitrosation Assay Procedure (NAP), a nitrosated metabolite was determined to be mutagenic in the Ames test. It was determined that this metabolite is formed in the stomachs of rats fed a high nitrite diet; therefore, in an effort to identify pathology associated with this mutagenic metabolite, toxicology and carcinogenicity studies were designed to include rats fed a high nitrite diet. As is discussed in the relevant sections, animals fed a high nitrite diet did not experience toxicity or develop tumors to a greater extent than their counterparts fed a standard diet.

Carcinogenicity

Three carcinogenicity studies were conducted, one in B6C3F1 mice and two in Han Wistar rats. In the mouse study, the incidence of pituitary adenomas was increased in MD F, and there were multiple non-neoplastic findings in the pituitary, but no increase in the incidence of hyperplasia. HD F experienced a 32% decrease in BW gain that resulted in a mean terminal BW that was 16% less than control. This degree of body weight difference is not likely to account for the absence of pituitary adenomas in HD F; nevertheless, the study may have been better designed if the MD of 65 mg/kg had been selected as the HD for F rather than 200 mg/kg. Harderian gland adenomas occurred in 13% of MD M, but the historical control range is up to 12%. Although there was an increase in Harderian gland adenomas in HD F, the incidence was within the historical control range. The doses selected for this study produced AUC's that were 11, 40, and 110X the human AUC achieved with the maximum allowable daily dose of 2 x 2.5 mg Naratriptan. Because Naratriptan is not highly metabolized (in mice, rats, and man the majority is excreted in urine and feces as parent compound), the use of Naratriptan AUC as justification for HD selection for males is generally acceptable, although there is the issue of the mutagenic N-nitroso metabolite. It was also determined in a 13 week dose ranging study that 400 mg/kg was too high of a dose because 4/30 mice died and mice experienced a 20% decrease in BW gain. As for the mutagenicity of the N-nitroso metabolite, which has been shown to be formed in the stomach of rats fed a high nitrite diet and in human gastric juice *in vitro* under high nitrite conditions, concern is mitigated by the

likelihood that patients experiencing a migraine will consume little food of any kind, let alone nitrite-preserved food.

The two rat carcinogenicity studies were of the same design, except that in one, rats were fed a standard diet, and in the other they were fed a nitrite supplemented diet in order to assess the oncogenic potential of any nitrosated metabolites. There were no dramatic differences between the studies. The major finding in both studies was functional stimulation of thyroid follicular cells as evidenced by hypertrophy, hyperplasia, and prominent cell pigmentation. Stimulation culminated in an increased incidence of benign follicular adenoma in HD M. In the standard diet study, an increased incidence of benign c-cell adenoma also occurred in the thyroids of HD M and F. In the nitrite-supplemented diet study, benign ganglioneuromas were observed in the thyroids of 2 HD F; although this tumor type is described by the sponsor as rare in Han Wistar rats, it occurs spontaneously in Sprague-Dawley rats. In addition to neoplasias in the thyroid, in the standard diet study there was an increased incidence of benign interstitial cell adenomas in the testes of HD M, although the absolute number of tumors was low. In the nitrite-supplemented diet study, there was an increased incidence of benign lymphocytic thymomas in all treated F groups, and an increased incidence of tubulostromal ovarian adenomas in HD F, although the absolute number of ovarian tumors was low. The high dose selected for the rat studies produced AUC's throughout the study that were >25 times the human AUC achieved with the maximum recommended daily dose of Naratriptan. Although the N-nitroso metabolite of Naratriptan is mutagenic in the Ames test, the use of AUC for dose selection may be acceptable because it is likely that patients experiencing a migraine will consume little food of any kind, let alone nitrite-preserved food. Dose selection for males is further supported by a dose ranging study in which testicular pathology was found at doses ≥170 mg/kg; resultant hormonal imbalances could potentially confound results of a carcinogenicity study.

In general, Naratriptan appears to have little oncogenic potential. All neoplasias that increased in incidence with treatment were benign, and all were adenomas except for the lymphocytic thymomas and thyroid ganglioneuromas found in the rat nitrite-supplemented diet study. The hyperplasia and benign neoplasias observed in the thyroids of HD rats may be an extension of the thyroid pathology observed in the 12 month dog study. In the dog study, hypertrophy of the thyroid follicular epithelium was observed in 1/3 HD M killed at 6 months and follicular cell adenoma occurred in 1 LD F killed at 12 months.

Labeling

Italics and strike-outs denote recommended changes to specific sections of the labeling.

CLINICAL PHARMACOLOGY:

Redacted 3

page(s) of trade secret and/or confidential commercial information

RECOMMENDATION

The NDA is approvable with respect to the pharmacology/toxicology portion pending labeling revision (see labeling recommendations made in the Summary and Evaluation).

Robin A. Huff, Ph.D.

cc: NDA20763
HFD-120
/G. Fitzgerald 9/7 10/1/97
/R. Huff
/L. Chen

APPEARS THIS WAY

APPEARS THIS WAY