FIGURE 1. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT 897-706-0
AVERAGE MATERNAL BODY WEIGHTS (GRAMS)

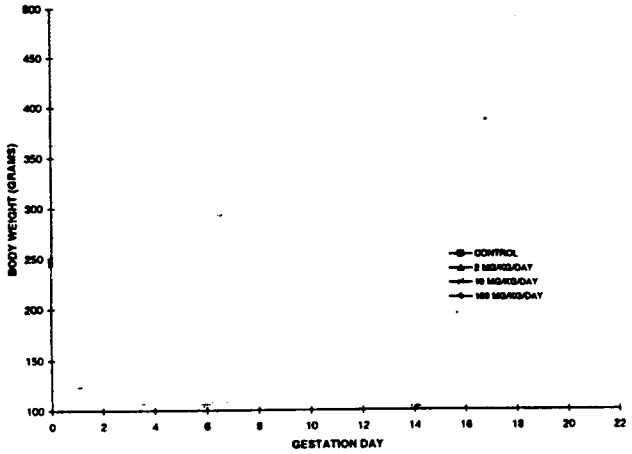
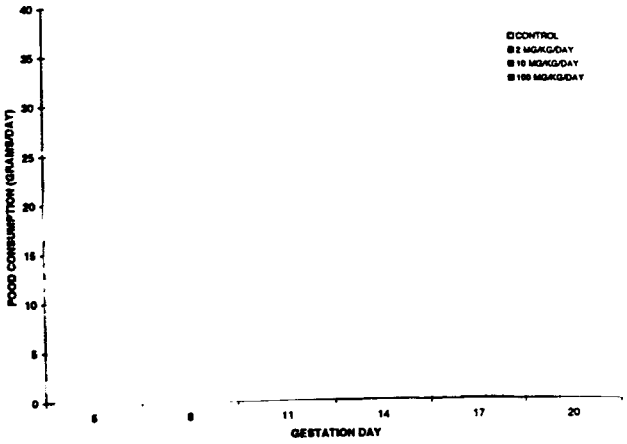


FIGURE 2. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT 897-706-0
AVERAGE MATERNAL FOOD CONSUMPTION (GRAMS/DAY)



Fetal - Fetal body weights were slightly (4%), but significantly reduced in the HD group (sponsor Table 4). No other treatment-related effects on embryo survival, or external, visceral or skeletal examinations were observed (sponsor Tables 5, 6 & 7). The incidences of incomplete ossification, particularly sternebrae, were increased in drug-treated animals, but a dose-relationship was not evident (sponsor Tab. 8).

TABLE 4. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #97-706-0

SUMMARY OF LAPAROTOMY DATA

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
FEMALES				
TOTAL FEMALES	25	25	25	25
PREGNANT	23	25	24	25
EXAMINED LIVE LITTER	23	25	24	25
RESORBED OR DEAD LITTER	0	0	0	0
DIED	0	0	0	0
SACRIFICED	0	0	0	0
NOT PREGNANT	2	0	1	0
LIVE	2	0	1	0
DIED	0	0	0	0
SACRIFICED	0	0	0	0
NOT BRED	0	0	0	0
CORPORA LUTEA				
CORPORA LUTEA	393	434	409	425
CORPORA LUTEA/PREGNANT FEMALE	17.1 ± 2.7	17.4 ± 2.4	17.0 ± 2.4	17.0 ± 1.7
% PERI-IMPLANTATION LOSS (LITTER MEAN)	8.5 ± 10.5	10.5 ± 14.6	5.4 ± 9.0	6.8 ± 11.3
IMPLANTS				
IMPLANTS	358	386	383	394
IMPLANTS/PREGNANT FEMALE	15.6 ± 2.3	15.4 ± 2.8	16.0 ± 1.5	15.8 ± 2.0
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	14	19	29	20
% RESORPTIONS/IMPLANTS (LITTER MEAN)	4.1 ± 4.9	5.0 ± 6.2	7.5 ± 12.4	5.1 ± 5.5
DEAD FETUSES	0	1	0	0
% DEAD FETUSES/IMPLANTS (LITTER MEAN)	0.0 ± 0.0	0.6 ± 2.9	0.0 ± 0.0	0.0 ± 0.0
% POSTIMPLANTATION LOSS (LITTER MEAN)	4.1 ± 4.9	5.6 ± 7.6	7.5 ± 12.4	5.1 ± 5.5
LIVE FETUSES				
LIVE FETUSES	344	366	354	374
FEMALES	165	192	170	198
MALES	179	174	184	176
SEX RATIO (LITTER MEAN)	0.48	0.53	0.48	0.53
LIVE FETUSES/PREGNANT FEMALE	15.0 ± 2.5	14.6 ± 2.9	14.8 ± 2.4	15.0 ± 2.1
LIVE FETAL WEIGHT (GM, LITTER MEAN)				
FEMALES	4.71 ± 0.31	4.73 ± 0.42	4.62 ± 0.37 NS	4.51 ± 0.25 S
MALES	4.96 ± 0.30	5.05 ± 0.40	4.86 ± 0.47 NS	4.76 ± 0.38 S

% PERI-IMPLANTATION LOSS = ((NO. CORPORA LUTEA - NO. IMPLANTS) / NO. CORPORA LUTEA) X 100
% POSTIMPLANTATION LOSS = ((NO. RESORPTIONS + NO. DEAD FETUSES) / NO. IMPLANTS) X 100
SEX RATIO = (TOTAL NO. LIVE FEMALE FETUSES/TOTAL NO. LIVE FETUSES)
S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE

TABLE 5. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #97-706-0
SUMMARY OF EXTERNAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
LIVE FETUSES/LITTERS EXAMINED		344/23	366/25	354/24	374/25
DEAD FETUSES/LITTERS EXAMINED		0	1/ 1	0	0
FETUSES WITH MALFORMATIONS		0	1	0	0
%, LM ±S.D.		0.00± 0.00	0.67± 3.3	0.00± 0.00	0.00± 0.00
LITTERS WITH MALFORMATIONS (%)		0	1 (4.0)	0	0
FETUSES WITH VARIATIONS		0	0	0	0
%, LM ±S.D.		0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
LITTERS WITH VARIATIONS (%)		0	0	0	0
PLACENTAL MORPHOLOGY					
NO. ABNORMAL PLACENTAS/TOTAL EXAMINED*		0/344(1)	0/366(1)	0/354	0/374
TYPE AND NUMBER OF FETAL					
ALTERATIONS %, LM	CLASS				
ANOPHTHALMIA	(M)	0	1 (0.67)	0	0
DISPLACED EAR	(M)	0	1 (0.67)	0	0
AGNATHIA	(M)	0	1 (0.67)	0	0
ASTOMIA	(M)	0	1 (0.67)	0	0
TAIL MALFORMATION	(M)	0	1 (0.67)	0	0

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION

* = NUMBERS IN PARENTHESES REPRESENT PLACENTAS FROM DEAD FETUSES OR LATE RESORPTIONS.

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TABLE 6. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #97-706-0
SUMMARY OF VISCERAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
THORACIC AND ABDOMINAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		176/23	187/25 [a]	184/24	193/25
DEAD FETUSES/LITTERS EXAMINED		0	1/ 1	0	0
FETUSES WITH MALFORMATIONS		0	3	1	0
%, LM ±S.D.		0.00± 0.00	1.4 ± 5.0	0.52± 2.6	0.00± 0.00
LITTERS WITH MALFORMATIONS (%)		0	2 (8.0)	1 (4.2)	0
FETUSES WITH VARIATIONS		6	0	5	1
%, LM ±S.D.		3.9 ± 8.0	0.00± 0.00	2.7 ± 6.5	0.57± 2.9
LITTERS WITH VARIATIONS (%)		5 (22)	0	4 (17)	1 (4.0)
CORONAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		176/23	187/25	184/24	193/25
FETUSES WITH MALFORMATIONS		0	1	0	0
%, LM ±S.D.		0.00± 0.00	0.50± 2.5	0.00± 0.00	0.00± 0.00
LITTERS WITH MALFORMATIONS (%)		0	1 (4.0)	0	0
FETUSES WITH VARIATIONS		0	0	0	0
%, LM ±S.D.		0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL					
ALTERATIONS %, LM	CLASS				
INTERRUPTED AORTIC ARCH	(M)	0	1 (0.44)	0	0
ABNORMAL ORIGIN SUBC. ART.	(M)	0	1 (0.44)	0	0
MISSING AZYGOS VEIN	(M)	0	1 (0.50)	0	0
HYDROURETER	(M)	0	1 (0.44)	0	0
HYPOPLASTIC SPLEEN	(M)	0	0	1 (0.52)	0
NASAL CAVITY MALFORMATION	(M)	0	1 (0.50)	0	0
INNOMINATE VARIATION	(V)	0	0	0	1 (0.57)
URETER VARIATION	(V)	5 (3.3)	0	4 (2.2)	0
FOCALLY HEMORRHAGIC ADRENAL	(V)	1 (0.62)	0	0	0
SPLENIC VARIATION	(V)	0	0	1 (0.52)	0

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION

a = FOR FETUS 7, DAM 97-2028, SEE POSTMORTEM REPORT.

TABLE 7. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #97-706-0
SUMMARY OF SKELETAL EXAMINATION OF FETUSES (EXCLUDING OSSIFICATION DATA)

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
TORSO AND LIMB EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		344/23	366/25	354/24	374/25
DEAD FETUSES/LITTERS EXAMINED		0	1/ 1	0	0
FETUSES WITH MALFORMATIONS		2	1	7	1
%, LM ±S.D.		0.58± 1.9	0.36± 1.8	1.9 ± 9.5	0.31± 1.5
LITTERS WITH MALFORMATIONS (%)		2 (8.7)	1 (4.0)	1 (4.2)	1 (4.0)
FETUSES WITH VARIATIONS		26	31	38	28
%, LM ±S.D.		7.7 ± 8.6	9.1 ± 8.3	10 ± 10	7.4 ± 9.1
LITTERS WITH VARIATIONS (%)		14 (61)	18 (72)	15 (62)	15 (60)
HEAD EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		168/23	179/25	170/24	181/25
DEAD FETUSES/LITTERS EXAMINED		0	0	0	0
FETUSES WITH MALFORMATIONS		0	0	0	0
%, LM ±S.D.		0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS		0	0	0	0
%, LM ±S.D.		0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL					
ALTERATIONS %, LM	CLASS				
CERVICAL VERTEBRA MALFORMATION	(M)	1 (0.31)	0	0	0
MISSING VERTEBRA	(M)	0	0	5 (1.4)	0
FUSED RIB	(M)	1 (0.31)	0	0	0
AGENESIS OF RIB	(M)	0	0	1 (0.28)	0
HYPOPLASTIC RIB	(M)	1 (0.27)	1 (0.36)	3 (0.83)	1 (0.31)
MISSHAPEN RIB	(M)	0	0	1 (0.28)	0
VERTEBRAL COUNT VARIATION	(V)	1 (0.26)	2 (0.97)	1 (0.42)	0
WAVY RIB	(V)	1 (0.26)	0	1 (0.28)	0
CERVICAL RIB	(V)	8 (2.4)	9 (2.4)	7 (2.0)	10 (2.7)
SUPERNUMERARY RIB	(V)	19 (5.7)	22 (6.6)	30 (8.1)	18 (4.6)

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION

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TABLE 8. MK-0462/L-783,540: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #97-706-0
SUMMARY OF FETAL OSSIFICATION DATA

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
TORSO AND LIMB EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	344/23	366/25	354/24	374/25
FETUSES WITH INCOMPLETE OSSIFICATION	5	15	23	14
%, LM ±S.D.	1.5 ± 2.9	4.0 ± 6.9	6.0 ± 10	4.1 ± 9.6
LITTERS WITH INCOMPLETE OSSIFICATION (%)	5 (22)	9 (36)	9 (38)	8 (32)
NUMBER OSSIFIED SACROCAUDAL VERTEBRAE LITTER MEAN ±S.D.	10.3 ± 0.8	10.3 ± 0.8	10.0 ± 0.7	9.9 ± 0.7
HEAD EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	168/23	179/25	170/24	181/25
FETUSES WITH INCOMPLETE OSSIFICATION	0	0	0	1
%, LM ±S.D.	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.57± 2.9
LITTERS WITH INCOMPLETE OSSIFICATION (%)	0	0	0	1 (4.0)
SITE AND NUMBER OF FETUSES WITH				
INCOMPLETE OSSIFICATION %, LM				
INCOMP. OSS. CERVICAL VERTEBRA	1 (0.27)	0	0	0
INCOMP. OSS. THORACIC VERTEBRA	1 (0.31)	1 (0.24)	2 (0.60)	2 (0.50)
INCOMP. OSS. SKULL BONE	0	0	0	1 (0.57)
INCOMP. OSS. RIB	0	0	1 (0.28)	0
INCOMP. OSS. STERNEBRA	3 (0.89)	14 (3.8)	21 (5.4)	12 (3.6)

(LM) = LITTER MEAN

SUMMARY

Background and Rationale

Migraine is a common neurological disorder that affects of males and of females. Rizatriptan (RIZ) is another member of the 5-hydroxytryptamine $_{1D}$ receptor agonist pharmacological class, exemplified by sumatriptan, that appears to be effective in the treatment of migraine and associated symptoms. According to the sponsor, RIZ has some characteristics that are more favorable than sumatriptan including higher bioavailability and more rapid onset of action.

Pharmacology

Biochemical studies with cloned or brain 5-HT receptors indicated that RIZ is a selective, high affinity, full agonist for the 5-HT_{1D} and 5-HT_{1B} subtypes (formerly designated the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors). RIZ showed modest binding affinity at the 5-HT_{1A} (Ki ~ 450 nM), 5-HT_{1E} (Ki ~ 170 nM), 5-HT_{1F} (IC_{50} = 230 nM) and 5-HT_7 (Ki = 430 nM) subtypes, but negligible activity at the 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_{5A} and 5-HT_6 subtypes (K_is > 5900 nM). The minor human urinary metabolite, N-monodesmethyl-RIZ (L-706,248), displayed a 5-HT receptor binding profile similar to that of RIZ, but the major indoleacetic acid metabolite (L-749,335) was inactive.

RIZ had moderate affinity for α_{2c} receptors (IC_{50}~700 nM), and weak affinity for α_{2a} and α_{2b} receptors (IC_{50}s ~2300 and 6000 nM, respectively). The minor human metabolite 6-hydroxy-RIZ was moderately active at α_{2a} and α_{2c}(IC_{50}s ~ 600 and 140 nM, respectively). The affinities of RIZ for alpha receptors were comparatively higher than those of sumatriptan (IC_{50}s > 10 μM at α_{2a} and α_{2b}; ~ 1300 nM at α_{2c}). The affinities of RIZ for any other receptors studied is not considered biologically significant.

RIZ and sumatriptan were compared in functional studies for their capacity to constrict vessels associated with antimigraine efficacy (meningeal artery) and vessels associated with side effects (coronary artery). The sponsor's meta-analysis suggested a more favorable profile with RIZ with respect to craniovascular:coronary artery selectivity. However, the magnitude of the difference was rather small, and is considered of questionable clinical significance.

In other *in vitro* functional studies, RIZ was a weak agonist at 5-HT_{1A} and rat 5-HT_{1B} receptors, and a weak partial agonist at 5-HT_{2A} receptors. RIZ was inactive at 5-HT_2, 5-HT_{2c}, M_1, M_2, M_3, and H_1 receptors.

The potential antimigraine efficacy of RIZ was assessed *in vivo* in studies of carotid blood flow in dogs and ferrets, and the rat neurogenic dural plasma extravasation model. In barbitone-anesthetized dogs, RIZ appeared to have marked vasoconstictive effects on the carotid vasculature (ED_{50} = 54 μg/kg, i.v.) at doses far lower than those required to constrict the coronary artery. However, the actual degree of selectivity was difficult to assess from the data presented (see p. 7 for details). In anesthetized ferrets, RIZ caused a dose-dependent decrease in carotid blood flow (ED50 = 20 μg/kg, i.v.), and the effect did not diminish with repeated dosing. In the rat neurogenic plasma extravasation model, RIZ caused a dose-dependent inhibition of extravasation evoked by electrical stimulation of the trigeminal nerve (ED_{50} = 31 μg/kg, i.v.). Oral doses of RIZ (3 & 10 mg/kg) blocked electrically-evoked dural blood vessel dilation in anesthetized rats, an effect that is theoretically due to prejunctional inhibition of neuroactive peptide release (i.e., CGRP, Substance P).

Potential centrally-mediated antimigraine actions were evaluated in electrophysiological studies of central trigeminal neurons. RIZ (1 & 3 mg/kg, i.v.) caused dose-dependent inhibition of trigeminal neuronal firing in response to noxious stimulation of the dura mater. The sponsor contends (in labeling) that central actions may contribute to the clinical antimigraine efficacy of RIZ. However, because of the low CNS penetrability of RIZ, it is unlikely (in the opinion of the reviewer) that the central levels necessary to produce an effect would be achieved at therapeutic doses.

Safety Pharmacology

The primary focus of the safety pharmacology studies was the cardiovascular system. The main effects observed were tachycardia and hypertension in conscious dogs, hypertension (without consistent tachycardia) in conscious monkeys, and sympatholytic effects in rats similar to that seen with other 5-$HT_{1B/D}$ agonists. In the conscious dog study (n = 2), a high oral dose of RIZ (5 mg/kg) caused marked, sustained increases in blood pressure (~40 mm Hg) and heart rate (~100 bpm; doubling of control level). A moderate dose of 1 mg/kg caused mild tachycardia, but no effect on blood pressure. Moderate, sustained increases in blood pressue and heart rate were evoked with repeated dosing of 2 mg/kg (1 every 2 hr for 3 doses). In anesthetized dogs, 0.3 mg/kg RIZ, i.v., caused mild, sustained (up to 60 min) hypotension and transient bradycardia, but did not consistently potentiate vagal influences on the heart. In two conscious rhesus monkeys, intravenous RIZ administration caused blood pressure increases of 31 and 54 mm Hg, but no consistent effects on heart rate; peak plasma levels associated with the high dose were 288 ng/ml. Central administration of RIZ to anesthetized rats did not decrease blood pressure or heart rate (a 5-HT_{1A} agonist effect), or evoke the "von Bezold-Jarisch" vagal reflex (a 5-HT_3 agonist effect). Like other 5-$HT_{1B/D}$ agonists, intravenous RIZ inhibited the pressor response to electrical stimulation of preganglionic sympathetic nerves, but not that evoked by exogenous NE. These results suggest that peripheral vasodilatory properties of RIZ (and related "triptans") are likely due to prejunctional inhibition of NE release and not a direct effect on the vasculature.

RIZ displayed minimal potential for causing significant CNS, GI or renal side effects in a limited series of assessments. RIZ was essentially devoid of CNS activity in rats and or mice. Monkeys exhibited mild sedation, hypothermia and transient emesis at high doses. Dogs appeared slightly more sensitive, and displayed mydriasis, head-shaking and behavioral activation after moderate oral doses (0.5-2.0 mg/kg). Gastric acid output and renal function in dogs were not notably affected by RIZ.

In *in vivo* drug interaction studies, RIZ also did not alter the cardiovascular responses of anesthetized dogs to amitriptyline, fluoxetine, propranolol, verapamil or dihydroergotamine.

Acute Toxicology

The acute oral and intravenous toxicity of RIZ was evaluated in mice and rats. The lowest lethal oral dose in mice, the more sensitive species, was approximately 250 times greater than the standard therapeutic dose in humans (10 mg) on a mg/m^2 basis. Signs of toxicity included hypoactivity, ataxia, tremors and convulsions.

Subchronic and Chronic Toxicology

Mouse Study

RIZ was administered by gavage (25, 125, 250 and 500 mg/kg/day; refered to as LLD, LD, MD, HD) to mice for 14 weeks. Two treatment-related deaths occurred in the HD group. Decedent animals exhibited gastrointestinal gaseous distention but no histopathological changes at necropsy. Transient hypoactivity

was observed in most HD and 1 MD animal during week 1. Body weight gain was decreased at ≥ 250 mg/kg, and food consumption was decreased at ≥ 125 mg/kg, mainly during the early part of the study. No notable treatment-related changes were evident in clinical pathology or at necropsy except for slightly increased in erythron at HD, and an increase in relative kidney weights (25%) in HDM.

RIZ toxicokinetics were determined in mice in a companion 5-week study. At the NOAEL of the toxicity study (25 mg/kg), plasma exposures exceeded human exposures by approximately 130-174 times based on Cmax, and 82-96 times based on AUC.

Dog Studies

Gavage adminstration of RIZ (0.2, 1.0 and 5.0 mg/kg/day) was generally well-tolerated when administered to beagle dogs in 14-week and 53-week studies. There were no treatment-related deaths in either study. Mydriasis occurred commonly at all dose levels in both studies. Transient weight loss and decreased food consumption were observed in 3/8 HD animals in the 14-week study, and a general tendency of lower weight gain in the HD animals was observed in the 53-week study. There were no other clear treatment-related effects in routine parameters including ophthalmology and EKG. Modest increases in liver weight (24-30%) were evident at termination of the 53-week study, but no signs of hypertrophy or hyperplasia were reported by the pathologist. Plasma exposures at the NOAEL (1.0 mg/kg/day) in the 14-week study exceeded human exposures by 5.2-6.3 times based on Cmax, and 2.2-2.5 times based on AUC. Toxicokinetics were not determined in the chronic study.

Rat Studies

The effects of subchronic and chronic gavage administration of RIZ were evaluated in rats at doses of 500, 1000 and 2000 mg/kg/day for 14-weeks, and 10, 50 or 250 mg/kg/day for 53-weeks. A high rate of mortality occurred in the 14-week study at the HD (3M, 5F), which led to the termination of this group on day 8. One MDM and 2 MDF also died during the study. No adverse necropsy findings were identified as associated with death; thymic "depletion" or necrosis were the only findings in the decedent animals. Clinical signs observed in the studies were ptosis (≥ 50 mg/kg), hypoactivity (≥ 500 mg/kg) and salivation (all dose levels). In the 14-week study, head tremors occured in animals treated with 1000 mg/kg beginning in week 5. Body weight gain was markedly reduced at this level (22-33%), coincident with reduced food consumption. Increases in alkaline phosphatase and relative liver weights occurred in both studies at doses ≥ 250 mg/kg, but were not accompanied by liver histopathological findings.

A NOAEL was not established in the 14-week study because of significant clinical signs at all doses. Plasma exposures at the LD exceeded human exposures by approximately 1000-fold based on Cmax, and over 2200-fold based on AUC. The NOAEL for the 53-week study was 50 mg/kg. Plasma exposures at this dose exceeded expected human exposures by 261 times based on Cmax, and 274 times based on AUC.

Reproductive Toxicology

The potential toxicity of RIZ to reproduction and development was assessed in GLP Segment II studies in rats and rabbits, and Segment I and III studies in rats. Non-GLP range-finding studies were conducted to determine doses for the definitive studies. In addition, Segment II studies of RIZ + the degradant L783,540 were conducted in rats and rabbits. While some "major" reproductive toxicities were observed in the range-finding studies (e.g. pup deaths in rats; resorptions and dead fetuses, one abortion in rabbits), the definitive study doses were notably lower. Hence, the treatment-related toxicities in the definitive studies were comparatively "minor" (maternotoxicity - decreased body weight; developmental toxicity - impaired body weight development). Small increases in the incidence of hypoplastic ribs were observed in the two of three rat studies in which skeletal exams were performed, but the overall incidence rate for the three studies (1.0%) is within an independent historical control database (MARTA) average. An increased incidence of missing lung caudate lobes was observed in the rabbit Segment II study of RIZ + the degradant, and is probably a developmental delay secondary to maternotoxicity. Neither finding is considered directly related to treatment.

Embryotoxicity

In the rat range-finding study, RIZ was administered by gavage to mated females on gestation day 6 through lactation day 20 at doses of 25, 100, 250, 500 mg/kg. Maternotoxicity was evident as a decrease in body weight gain during gestation at $\geq$ 100 mg/kg. Pups deaths were significantly increased in the 500 mg/kg group on post-natal days 1-3 (12.1% vs. 1.1% in controls), and pup body weights were dose-dependently decreased during lactation. The sponsor's selection of 100 mg/kg as the high dose for definitive embryotoxicity and female fertility studies was apparently based on decreased maternal body weight gain.

In the definitive rat embryotoxicity study, RIZ (2, 10, 100 mg/kg) was administered by gavage to mated females during organogenesis (6-17 of gestation). Maternal body weight gain was significantly reduced at the HD (100 mg/kg) during gestation, and a slight, but statistically significant decrease in live fetal weight was apparent in HD offspring. The litter incidence of hypoplastic (1.55%) and cervical (2.1%) ribs in HD fetuses was slightly higher than controls, and higher than the MARTA database average (1.08% for hypoplastic ribs; 0.615% for cervical ribs). The sponsor did not consider these findings treatment-related as the incidence rates were within their historical range. The NOAEL for maternotoxicity and developmental toxicity is 10 mg/kg/day based on body weight impairments. In a companion toxicokinetic study, maternal exposures at the HD were higher than expected human exposures by 640 times based on AUC, and 322 times based on Cmax. At the LD, the ratios of maternal rat to human exposures were 4.2 and 7.0 based on AUC and Cmax, respectively. Toxicokinetic data were not obtained at the MD (i.e., the NOAEL). Determination of fetal:maternal plasma ratios demonstrated placental transfer of RIZ. Data from rats treated through lactation indicated that RIZ is secreted extensively into milk.

A rat embryotoxicity study of RIZ + the degradant (2, 10, 100 mg/kg; 98:2 mixture) did not reveal any additional toxicities. The incidence of hypoplastic ribs was similarly low in all treatment groups.

Embryotoxicity was assessed in rabbits by administering RIZ during organogenesis on gestation days 6-18. In a range-finding study of 5, 25 and 100 mg/kg/day, maternotoxicity was evident at $\geq$ 25 mg/kg as decreased body weight gain, decreased food consumption and slow pupillary reflex. Additional signs/toxicities at 100 mg/kg were weight loss, lethargy and one abortion. Fetotoxicity was evident at 100 mg/kg as an increase in resorptions and dead fetuses, and a decrease in fetal weights. Fetotoxicity

may have been related to cessation of food intake by dams during gestation. In the definitive study of 5, 10 and 50 mg/kg/day, maternal toxicities included body weight loss, decreased food consumption, and mydriasis. There were no treatment-related effects on pregnancy parameters, fetal weights, external morphology or skeletal examinations. Thus, RIZ was devoid of teratogenic effects in rabbits at a maternotoxic dose of 50 mg/kg. The NOAEL for F_0 is 10 mg/kg based on decreased body weight and food consumption. The NOAEL for F_1 is 50 mg/kg. In a companion toxicokinetic study, maternal exposures at the LD (below the NOAEL for F_0) exceeded expected human exposures by 12 times based on Cmax, and 9 times based on AUC. Maternal plasma exposures at the NOAEL for F_1 exceeded expected human exposures by 292 times based on Cmax and 325 times based on AUC.

A rabbit embryotoxicity study was also conducted on a mixture of RIZ plus the degradant L-783,540 (5, 10, 50 mg/kg of a 98:2 mixture). Findings that were not observed in studies of RIZ alone were slight, but significant decreases in live fetal weights at the HD, and an increased incidence of missing lung caudate lobes in HD fetuses (fetal incidence = 12.0 % in HD, 4.0% in control). A slight (nonsignificant) reduction in fetal weights occurred in the study of RIZ alone; thus, the finding is not considered due to the degradant, but an interstudy variation. Similarly, a slightly greater degree of maatrnotoxicity (reduced body weight) in the degradant study may have led to a developemtal delay with respect to lung development. Further, a direct degradant effect on the developing fetus is considered unlikely since the placental transfer of the quaternary amine may be limited.

Fertility

Potential effects on female rat fertility were assessed after gavage administration of RIZ (0, 2, 10 and 100 mg/kg/day) from day 14 prior to mating through gestation day 20, or through lactation day 20. Mating in the HD group was slightly delayed, possibly due to persistent diestrus. MD and HD pups in the natural delivery group displayed treatment-related decreases in body weight gain during lactation. Embryofetal findings consistent with the Segment II study were hypoplastic ribs in 2 HD fetuses (incidence rate = 1.4%). No other treatment-related developmental impairments or abnormalities were seen in the F_1 or F_2 generations. The NOAEL for the F_0 is 10 mg/kg based on possible estrus delays at the HD. The NOAEL for F_1 is 2 mg/kg based on impaired pup body weight development.

Effects on male rat fertility were assessed after gavage RIZ administration (0, 5, 35 and 250 mg/kg/day) for 70 days prior to mating through the cohabitation period. Body weight gain was significantly reduced in HD animals by 12% on weeks 1-10, and 31% on weeks 11-15, but no impairments of male reproductive performance or notable necropsy findings were observed. Untreated female partners showed no evidence of altered reproduction or pregnancy, and there was no evidence of treatment-related changes in fetal development. The NOAEL for toxicity in treated males (decrease body weight gain) was 35 mg/kg. The NOAEL for impairment of reproductive performance was > 250 mg/kg. These studies suggest that RIZ does not present a significant risk to reproductive performance in male rats.

Perinatal/Postnatal Development

RIZ (2, 10, 100 mg/kg/day) was administered to mated female rats from gestation day 6 to lactation day 20. Maternotoxicity was evident as transiently reduced body weight gain at the HD (16% on days GD15-20). The only developmental impairment was reduced body weight gain in HD pups throughout lactation, and in MDF pups on PND 0. A relatively large number of pup deaths (14) were observed in the MD on PND 0. The deaths were not commented on by the sponsor, but the absence of a significant number of

pup deaths at the HD argues against a treatment-relationship. The NOAELs were 10 mg/kg/day for F_0, and 2 mg/kg for F_1 based on decreased body weight gain or development.

Mutagenicity

A complete battery of genotoxicity studies was conducted (Ames test, chromosomal aberrations *in vitro* and *in vivo*, mutation in mammalian cells). A test for DNA strand breaks was also included. Except for the in vivo chromosomal aberration assay, all studies were consistent with OECD guidelines. RIZ was negative in all studies.

Dosage selection in the *in vivo* chromosomal aberration study was not consistent with OECD guidelines. The high dose in that study was 125 mg/kg (single gavage administration). In an acute oral toxicity study, severe clinical signs and lethality were not observed at doses lower than 625 mg/kg. Clearly, the animals could have tolerated a higher single dose. The absence of a notable (50%) reduction in mitotic index and any evidence for distribution of RIZ to the bone marrow further suggest that the 125 mg/kg was inadequate. However, toxicokinetic data indicated a wide exposure margin between the 125 mg/kg dose in mice and anticipated human exposure (640-fold). Coupled with the absence of positive findings in any other assay, and the *MULTICASE* QSAR prediction that RIZ is not a rodent carcinogen, an additional study of higher doses is not warranted.

Carcinogenicity

The carcinogenic potential of orally administered RIZ was assessed in a 100-week study in mice (gavage doses: 0, 2, 25, 125 mg/kg/day), and in a 106-week study in rats. Because RIZ is relatively non-toxic to rodents, dosage selection was based on plasma exposure data from subchronic toxicity and toxicokinetic studies. Animal plasma exposures from those studies were 314-687 times the expected human exposure, far greater than the 25-fold ratio recommended by ICH guidances.

Neither study provided evidence for tumorigenic potential of RIZ in rodents under appropriate test conditions according to either the sponsor's or the Agency's analyses. There were no notable effects of RIZ on body weights that would have impacted study interpretation. According to the Agency's survival analysis, there was no evidence of a treatment-related mortality trend. No specific drug-related causes of death were identified.

Pharmacokinetics and Metabolism

The single-dose pharmacokinetics and elimination of RIZ were evaluated in rats and dogs. The intravenous studies indicated a short half-life, a plasma clearance rate similar to hepatic flow, and a moderately high volume of distribution. Oral bioavailability ranged from , in dogs and , in rats. Absorption was usually rapid . Excretion was essentially complete by 24 hrs. Renal excretion was the primary route after either i.v. or p.o. administration to dogs, and i.v. administration to rats. Urinary and fecal excretion was comparable after oral administration to rats. The urinary:fecal excretion results were generally confirmed by a biliary excretion study in bile duct-cannulated rats and dogs (Ref. r2), except that a similar percent of dose was excreted in rat bile after either route

A small, single dose pharmacokinetic study in male volunteers determined that bioavailability of RIZ was only 47% despite nearly complete absorption, possibly because of significant first pass metabolism. Peak levels were achieved at after oral administration. Most of the radiolabel was excreted in urine within 24 hr.

In vivo studies of RIZ metabolism in rats, dogs, mice, rabbits and humans identified several qualitatively similar pathways among species. The major metabolic routes for RIZ were oxidative deamination to the indoleacetic acid (RIZ-IAA), aromatic hydroxylation at 6-position of the indole ring (6-hydroxy-RIZ), N-oxidation of the tertiary amine (N-oxide), N-demethylation and sulfate conjugation of 6-hydroxy-RIZ.

Following oral (10 mg) or intravenous (3 mg) administration of [^{14}C]-RIZ to humans, RIZ-IAA appeared as the major drug-related species in plasma ( ) and urine ; the parent compound was the second most abundant species 25% in plasma). Smaller amounts of RIZ-N^{10}-oxide (<10%), the 6-sulfate conjugate and N-demethylated metabolites (<6%; tentative identification) were present. In dogs, comparable amounts of 3 metabolites (RIZ-IAA, RIZ-N^{10}-oxide, 6-hydroxy-RIZ-N^{10}-oxide; ~15%) were identified in urine at levels greater than those of the parent compound (7.4%) [plasma metabolites were not studied in dogs]. In rats, the parent compound was major urinary drug-related species following oral (37%) or intravenous administration (52%); the N^{10}-oxide was present at higher levels (than RIZ-IAA (~10%). The profile in rat plasma 60 min post-dose (3 mg/kg, p.o.) was RIZ-IAA (45%) > RIZ (30%) > RIZ-N^{10}-oxide (17%). In mice, RIZ-IAA was by far the most abundant species in plasma at 30-60 min post-dose (3 mg/kg, p.o. However, the parent compound was the most abundant species in 0-24 hr mouse urine (54%; vs. 22% for RIZ-IAA and 9% for RIZ-N^{10}-oxide). Rabbits were distinct from other species in that N-desmethyl-RIZ was the major plasma metabolite, although it was present at far lower levels than the parent compound.

The biological activity of some of the RIZ metabolites was assessed in 5-HT receptor binding assays. Only the minor N-desmethyl metabolite was similar to RIZ in its 5-HT_{1D} and $_{1A}$ affinities. The major metabolite (RIZ-IAA; L-749,335) was devoid of 5-HT receptor affinity.

In vitro metabolizing fractions from various tissues (rat liver, lung and kidney microsomes, human and dog microsomes) generated a less complex profile and far lower levels of metabolites than that expected based on the *in vivo* studies. Human liver S9 converted approximately 5% of the parent compound to the IAA metabolite. The other major human *in vivo* metabolite, RIZ-N^{10}-oxide, was not identified as an S9 product. These determinations are important for assessing the validity/relevance of genotoxicity studies with the S9 fraction. *In vitro* studies also determined that the oxidative deamination of RIZ is mediated primarily by MAO-A rather than MAO-B.

Because of the importance of oxidative deamination by MAO-A in the disposition of RIZ, clinical studies addressed the potential interaction of RIZ with MAO inhibitors. The MAO-A inhibitor moclobemide markedly decreased the formation of the IAA metabolite and increased the exposure to RIZ, suggesting that an important drug interaction may exist between RIZ and selective inhibitors of MAO-A. The β-blocker propranolol also appeared to have significant inhibitory effects on RIZ oxidative deamination *in vitro*.

Plasma protein binding by RIZ was similar among species ranging from 14-27%. RIZ partitioned into rat, dog and human erythrocytes. A distribution study in rats indicated that highest levels of radioactivity were associated with organs of absorption and elimination. No unusual tissue accumulations were observed. RIZ binding to melanin-containing tissues was not assessed.

Special Studies

A series of studies were conducted to assess the toxicology of a potential degradant in the RAPIDISC preparation if MAXALT. The degradant, a methylated quaternary salt of RIZ, has been detected at levels up to 0.4% after 52 weeks of storage at 25 and 30° C. At higher temperatures (40° C), levels of 0.8% have been observed after 6 months. The sponsor has qualified this degradant in toxicology studies at a level of 2%. Studies included 14-week oral toxicity studies in rats and dogs, oral developmental toxicity studies in rats and rabbits, and genotoxicity studies (Ames test, *in vitro* chromosomal aberration assay, *in vitro* alkaline elution assay). In all studies, the ratio of RIZ to degradant was 2:98. No novel toxicities were introduced by the inclusion of the degradant. Aside from the equivocal findings of the rabbit Segment II study , no potentiation of toxicity by the degradant was observed in any study.

EVALUATION

Rizatriptan benzoate is a new molecular entity of the "triptan" class intended for the treatment of migraine. It is closely related to several compounds recently reviewed or currently under review by this division including sumatriptan, naratriptan, and zolmitriptan. Because these compounds are so similar chemically (tryptamine derivative) and pharmacologically (5-$HT_{1B/D}$ agonists), a similar toxicological profile might also be expected. A table on page 106 summarizes some of the major toxicological findings that have appeared in approved (or approvable) labeling of these compounds, and compares them with RIZ.

Clearly, the major labeling issue with RIZ centers on the Pregnancy section. The sponsor proposes labeling RIZ as category B based on the relatively modest toxicities observed in the definitive studies. However, RIZ produced some significant toxicities (i.e., embryolethality) in range-finding (non-GLP) studies, which raises the questions of whether adequate doses were tested in the definitive studies. Two lines of evidence support the position that high dose selection was valid:

1) slight maternotoxic effects were observed in the definitive studies
2) the relative exposures in pregnant animals at the HD were high (rat: 292 times human AUC; rabbit: 148 times human AUC; both species: the HD was 27 times the MRHD of 30 mg/day on a mg/m^2 basis)

In comparison to the related compounds, RIZ appears to have lower reproductive toxicity potential than sumatriptan and naratriptan in both species, and zolmitriptan in rabbits. There were no indications of an association between RIZ administration and fetal malformations or variations, which have been observed with the other "triptans". However, the developmental impairments observed after RIZ treatment during pregnancy (i.e., decreases in fetal weights in the rat and rabbit [RIZ + degradant] developmental toxicity studies) and lactation (decreases in the pup body weight gain during lactatation) may merit a Pregnancy C classification, particularly given the intended patient population (primarily female). Coupled with the toxicities encountered in the dose range-finding studies, and the questionable validity of the definitive studies because of the use of insufficient doses, a Pregnancy C classification is further supported.

A similar strategy of selecting definitive study high doses to be near the No-Effect level in range-finding studies was utilized in the dog toxicology studies. The sponsor considered the clinical signs caused by a 10 mg/kg dose in an exploratory as unacceptable (continuous barking, hyperactivity, mydriasis, and scleral redness). Thus, 5 mg/kg was the high dose for an 18-day dog study, in which similar, but less severe signs were observed. The 5 mg/kg dose was the high dose in the 14-week study and 53-week studies; mydriasis and limited instances of transient body weight impairments were observed. Toxicokinetics in the 14-week study indicated that plasma exposures at the HD exceeded expected human exposures by a fair margin ($\geq$ 37-fold based on Cmax; $\geq$ 16-fold based on AUC). While the 14- and 53-week studies were a rather poor assessment of the toxicological profile of RIZ because of the relatively mild toxicological challenge, they are acceptable based on the the exposure margin and body weight effects.

The rodent toxicology and carcinogenicity study packages were acceptable. High doses were appropriately selected at or near the MTD, and high relative exposures were demonstrated. No serious or unusual toxicological or tumorigenicity concerns were raised by these studies.

The adequacy of the mutagenicity testing was questionable with respect to the dose used in the *in vivo* chromosomal aberration study in mice (125 mg/kg). According to OECD guidelines, the dose selected should produce bone marrow toxicity, or other signs of toxicity such that higher levels would produce lethality. No toxicity was evident in the study animals, and the lowest lethal dose in an acute toxicity study in mice was 625 mg/kg. On this basis, the study could be considered unacceptable. However, mouse exposures at the 125 mg/kg dose in a 5-week toxicokinetic study were 640 times the human exposure. Because of this wide margin, the absence of positive findings in any other mutagenicity or carcinogenicity study, and the *MULTICASE* QSAR prediction (see Appendix 1) that RIZ is not a rodent carcingen, an additional study chromosomal aberration study of higher doses is not warranted.

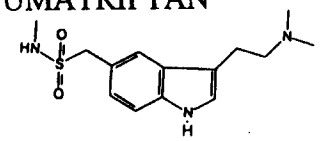
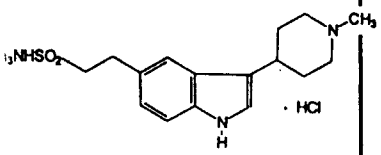
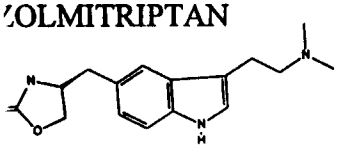
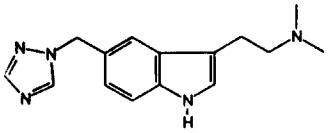
The pharmacokinetic and metabolism studies suggested general similarities among species in the disposition and handling of RIZ. Metabolism of RIZ is qualitatively similar among species, and humans do not appear to form any significant metabolites that weren't generated in animals. One deficiency of the submission is the absence of melanin binding studies. Statements are present in the labeling of other triptans noting their melanin-binding properties. Since RIZ is expected to bind melanin because of its basic properties and chemical similarities to the other triptans, a "class-effect" statement should be included in labeling under "PRECAUTIONS".

A companion NDA for a RAPIDISC formulation containing RIZ was submitted, which presented a degradant issue for evaluation. The degradant, the N-methylated quaternary ammonium salt of RIZ, was evaluated in appropriate subchronic, genetic and reproductive toxicology studies. No additional or unusual toxicologies were associated with the degradant when tested at a level of 2%, a level higher than that observed under any stability testing conditions.

In conclusion, the application contains adequate information on the nonclinical pharmacology and toxicology of RIZ to be considered approvable with appropriate labeling. The labeling should address the deficiencies in the application, most notably those related to the reproductive toxicology testing. The deficiencies generally resulted from the use of doses that are considered too low to completely characterize the toxicological profile of RIZ. While this is considered a flaw in the scientific approach of the sponsor and was not limited to the reprotoxicology program, the fact that RIZ exposures in animals were generally well in excess of expected human exposures provides the primary basis for considering the studies adequate and the application approvable.

Comparative Toxicology Findings with Triptans

[values in parentheses represent the multiple of human dose (HD; mg/m^2) or exposure (HE; AUC) at which the effect occurred]

	General Tox	Reprotox	CA	Genetox
UMATRIPTAN 	dog: corneal opacity	rat: ↓ fertility (5x HD); vessel abs., ↓ pup surv. (25x HD); malformations (50x HD); rabbit: embryolethality (18x HD); vascular & skeletal abs. (rabbits; 10x HD)	mouse: no tumors (40x HE); rat: no tumors (15x HD)	no positive tests
IARATRIPTAN 	dog: corneal stippling	rat: preimplant loss (70x HE); embryolethality (470x HE); fetal variations (11x HE); tremors in F1 (11x HE); ↓ estrus cyclicity (230x HE); gonadal atrophy (470 x HE) rabbit: embryonic death, fetal variations (Dutch; 4x HD);↓ fetal wts, fetal variations (NZ; 2.5 x HD)	mouse: no tumors (110x HE); rat: thyroid follicular cell adenomas (M; 30x HE)	no positive tests
ZOLMITRIPTAN 	none	rat: embryolethality (280-5000x HE); hydronephrosis in F_1 (1100x HE); rabbit: embryolethality (11x HE); fetal malformations and variations (42x HE)	mouse: no tumors (800x HE); rat: thyroid follicular cell adenomas (M; 3000x HE)	Ames pos (+ S9); clastogenic *in vitro* (+ or - S9);
RIZATRIPTAN 	none	rat: <u>Def. study:</u> ↓ pup wt gain (2.7x HD); ↓ fetal wt, prolonged diestrus (292x HE); <u>RF study:</u> pup deaths (400x HD); rabbit: <u>Def. study (+ deg):</u> ↓ fetal wt (148x HE); <u>RF study:</u> abortions, resorptions, dead fetuses, ↓ fetal wt (53x HD)	mouse: no tumors (314x HE); rat: no tumors (519x HE)	no positive tests

[Almotriptan, another related compound currently active under IND , also causes significant reprotoxicities (female rat infertility; embryolethality in rats and rabbits) and thyroid follicular cell hypertrophy in rats, possibly a precursor stage for thyroid neoplasia]

Comparative Rizatriptan Exposures Among Species

Species	Duration (time of measure)	Dose	Cmax (ng/ml)	AUC	
				(µg.hr/ml)	ratio to MRHD
Human	-	30 mg (MRHD)	35	0.16	-
Dog	14 wk (day 90)	0.2 M	24	0.02	0.1
		0.2 F	20	0.02	0.1
		1.0 * M	128	0.18	1.1
		1.0 * F	143	0.16	1.0
		5.0 M	850	1.17	7.3
		5.0 F	1002	1.22	7.6
Rat	14 wk (LD, MD:wk 4 HD: d8)	500 M	22000	163	1019
		500 F	25000	215	1344
		1000 M	37000	525	3281
		1000 F	50000	424	2650
		2000 M	42000	-	-
		2000 F	51000	-	-
	53wk (wk 21)	10 M	2000	3	19
		10 F	2000	3	19
		50 * M	6000	20	125
		50 * F	6000	20	125
		(125)[a] M		50	312
		(125)[a] F		51	319
		250 M	24000	116	725
		250 F	20000	105	656
Mouse	5 wk	25 * M	4000	7	44
		25 * F	3000	6	38
		125 M	14000	32	200
		125 F	12000	31	194
		250 M	31000	74	462
		250 F	19000	70	438
		500 M	38000	162	1012
		500 F	25000	122	762
Preg Rat	Developmental Toxicity (d. 20)	2	160	0.31	2
		10 *(F_0F_1)	n.d.	n.d.	-
		100	7400	46.7	292
Preg Rabbit	Developmental Toxicity (d. 18)	5	270	0.63	4
		10 * (F_0)	n.d.	n.d.	-
		50 * (F_1)	6720	23.7	148

* NOAEL; **MRHD** = 30 mg/day (AUC ~ 0.16 µg.hr/ml); n.d. = no data

[a] Interpolated value based on linear kinetics for HD in the 2-year carcinogenicity study

4 Page(s) Redacted

DRAFT LABELING

~~observed.~~ Rizatriptan is extensively excreted in rat milk.

It is not known whether ~~this drug~~ rizatriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MAXALT is administered to women who are breast-feeding.

RECOMMENDATIONS

1. The NDA is approvable.

2. Revise labeling as recommended in the preceding section.

/S/

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Original NDA 20864
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