CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20864/20865

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-864

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 04MAY98

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	*30JUN97*	*30JUN97*	*03JUL97*
AMENDMENT	*11SEP97*	*12SEP97*	*12SEP97*
AMENDMENT	*30OCT97*	*31OCT97*	*05JAN98*
AMENDMENT	*31OCT97*	*03NOV97*	*05JAN98*
AMENDMENT	*26DEC97*	*29DEC97*	*05JAN98*
AMENDMENT	*29DEC97*	*30DEC97*	*05JAN98*
AMENDMENT	*11FEB98*	*12FEB98*	*18FEB98*
AMENDMENT	*05MAR98*	*06MAR98*	*11MAR98*
AMENDMENT	*13MAR98*	*13MAR98(FAX)*	*19MAR98*
AMENDMENT	02APR98	DESK COPY	04APR98

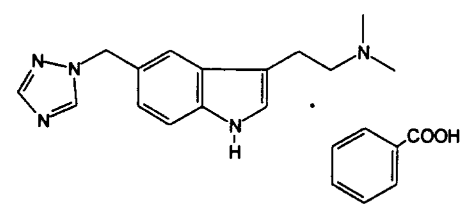
NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486

DRUG PRODUCT NAME:
Proprietary: MAXALT® Tablets
Nonproprietary/Established/USAN: rizatriptan (benzoate) [USAN, 1997]
Code Name/#: MK-0462; L-705,126
Chem. Type/Ther. Class: 1S

DESI / Patent Status: no DESI issues. patent 5,298,520, expires 28 JAN 2012

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: tablets
STRENGTHS: 5.0, 10.0 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: XXX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, CAS NUMBER:
N,N-dimethyl-5[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indole-3-ethanamine benzoate (salt)



$C_{15}H_{19}N_5 \cdot C_7H_6O_2$ mw = 391.47, 269.5 (free base)

CONCLUSIONS & RECOMMENDATIONS:

cc: Orig. NDA
HFD-120/Division File
HFD-120/DJBates/04MAY98
HFD-120/LChen/CSO
HFD-810/120/RSeevers/Init.: /S/
HFD-810/JSimmons
HFD-810/CHoiberg

/S/

Doris J. Bates, Ph.D., Review Chemist
Filename: 20864.nda\review.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-865

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 18MAY98

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	30JUN97	30JUN97	03JUL97
AMENDMENT	11SEP97	12SEP97	12SEP97
AMENDMENT	26DEC97	29DEC97	05JAN98
AMENDMENT	29DEC97	30DEC97	05JAN98
AMENDMENT	11FEB98	12FEB98	18FEB98
AMENDMENT	05MAR98	06MAR98	11MAR98
AMENDMENT	06MAR98	11MAR98	13MAR98
AMENDMENT	13MAR98	16MAR98	19MAR98
AMENDMENT	02APR98	DESK COPY	04APR98
AMENDMENT	02APR98	DESK COPY	04APR98
AMENDMENT	15MAY98	DESK COPY	15MAY98

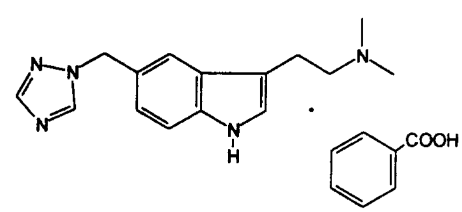
NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486

DRUG PRODUCT NAME:
- **Proprietary:** MAXALT® RPD
- **Nonproprietary/Established/USAN:** rizatriptan (benzoate)
- **Code Name/#:** MK-0462; L-705,126
- **Chem. Type/Ther. Class:** 1S

DESI / Patent Status: no DESI issues. patent 5,298,520, expires 28 JAN 2012

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: Zydis® orally disintegrating tablet
STRENGTHS: 5.0, 10.0 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: XXX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, CAS NUMBER:
N,N-dimethyl-5[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-3-ethanamine benzoate (salt)
$C_{15}H_{19}N_5 \cdot C_7H_6O_2$ mw = 391.47, 269.5 (free base)



CONCLUSIONS & RECOMMENDATIONS: May be approved for CMC.

cc: Orig. NDA
HFD-120/Division File
HFD-120/DJBates/18MAY98
HFD-120/LChen/CSO
HFD-120/RSeevers/Init.: /S/
HFD-810/JSimmons
HFD-810/CHoiberg

/S/
Doris J. Bates, Ph.D., Review Chemist
Filename: 20865.nda\review.003

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: 4/16/98
I called Dr. Goldman to bring her up to date on the issue of the name of the dosage form. I told her that it is complicated by the fact that two drugs are already approved with the rapidly disintegrating tablet dosage form name. I told her that I will be discussing this issue at a 5 DD's meeting in the very near future and that I will keep her informed. She asked if a change in the dosage form name is recommended, whether we would require the already approved drugs to change as well. I told her that I believe that we would do that to maintain consistency, probably asking them to change at the next printing. I told her that I could not provide a specific date by which I could give a definite answer, because the issue is one which has to be addressed in a center-wide fashion. She told me that she understood and thanked the agency for giving them the heads-up to avoid printing labeling material which would have to be discarded. /S/ 4/16/98 **Name:** Robert H. Seevers **HFD-120**	**NDA #:** 20-865 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Maxalt **Firm Name:** Merck **Name and Title of Person with whom conversation was held:** Bonnie Goldman **Phone:** 610-397-2383

APPEARS THIS WAY ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-864

CHEMISTRY REVIEW: # 2 **DATE REVIEWED:** 25MAR98

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	*30JUN97*	*30JUN97*	*03JUL97*
AMENDMENT	*11SEP97*	*12SEP97*	*12SEP97*
AMENDMENT	30OCT97	31OCT97	05JAN98
AMENDMENT	31OCT97	03NOV97	05JAN98
AMENDMENT	26DEC97	29DEC97	05JAN98
AMENDMENT	29DEC97	30DEC97	05JAN98
AMENDMENT	11FEB98	12FEB98	18FEB98
AMENDMENT	05MAR98	06MAR98	11MAR98
AMENDMENT	13MAR98	13MAR98(FAX)	19MAR98

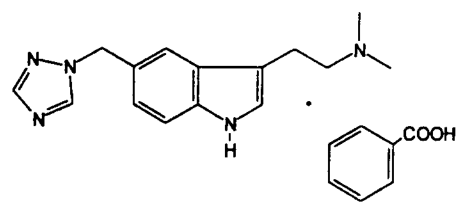
NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486

DRUG PRODUCT NAME:
- **Proprietary:** MAXALT® Tablets
- **Nonproprietary/Established/USAN:** rizatriptan (benzoate) [USAN, 1997]
- **Code Name/#:** MK-0462; L-705,126
- **Chem. Type/Ther. Class:** 1S

DESI / Patent Status: no DESI issues. patent 5,298,520, expires 28 JAN 2012

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: tablets
STRENGTHS: 5.0, 10.0 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: XXX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, CAS NUMBER:
N,N-dimethyl-5[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indole-3-ethanamine benzoate (salt)



$C_{15}H_{19}N_5 \cdot C_7H_6O_2$ mw = 391.47, 269.5 (free base)

CONCLUSIONS & RECOMMENDATIONS:

cc: Orig. NDA
HFD-120/Division File
HFD-120/DJBates/25MAR98
HFD-120/LChen/CSO
HFD-810/120/RSeevers/Init.: /S/ 5/31/98 6/3/98
HFD-810/JSimmons/Init.:
HFD-810/CHoiberg/Init.:

/S/ 25Mar98
Doris J. Bates, Ph.D., Review Chemist 03Jun98
Filename: 20864.nda\review.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-864

CHEMISTRY REVIEW: # 1 **DATE REVIEWED:** 31OCT97

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	30JUN97	30JUN97	03JUL97
AMENDMENT	11SEP97	12SEP97	12SEP97

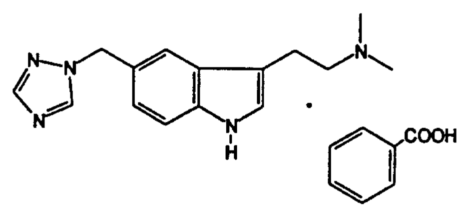
NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486

DRUG PRODUCT NAME:
Proprietary: MAXALT® Tablets
Nonproprietary/Established/USAN: rizatriptan (benzoate)
Code Name/#: MK-0462; L-705,126
Chem. Type/Ther. Class: 1S

DESI / Patent Status: no DESI issues. patent 5,298,520, expires 28 JAN 2012

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: tablets
STRENGTHS: 5.0, 10.0 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: XXX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, CAS NUMBER:
N,N-dimethyl-5[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indole-3-ethanamine benzoate (salt)
$C_{15}H_{19}N_5 \cdot C_7H_6O_2$ mw = 391.47, 269.5 (free base)



CONCLUSIONS & RECOMMENDATIONS: Comments and deficiencies
Approvable. Further information needed.

cc: Orig. NDA
HFD-120/Division File
HFD-120/DJBates/31OCT97
HFD-120/LChen/CSO
HFD-120/MGuzewska/Init.: /S/ 11.25.97

/S/

Doris J. Bates, Ph.D., Review Chemist
Filename: 20864.nda\review.001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20864/20865

PHARMACOLOGY REVIEW(S)

MEMO

TO: **NDA 20864 and 20865, Maxalt tablets and orally disintegrating tablets**
FROM: **Glenna G. Fitzgerald, Ph.D, Pharmacology Team Leader, HFD-120**
DATE: **May 29, 1998**
SUBJECT: Response to Merck's labeling revisions of May 14,1998

Dr. Thomas Steele has reviewed the sponsor's revisions to our proposed labeling for Maxalt (see his memo of May 20, 1998). Dr. J.E. Fisher has also reviewed the pregnancy labeling as well as the sponsor's Reference 4 which provides their rationale for recommended changes in the Impairment of Fertility and Pregnancy sections. His recommendations are incorporated into Dr. Steele's memo. The major issue is their contention that Maxalt should be Pregnancy Category B rather than C.

I have the following comments, and have underlined recommended changes to the sponsor's proposed labeling, and/or recommended final labeling where sections have been extensively revised.

1 Page(s) Redacted

DRAFT LABELING

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/S/

Glenna G. Fitzgerald, Ph.D.

NDA 20-864, 20-865

c.c. Div. File/ Levin/Steele/Fitzgerald/Fisher/Chen

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ON ORIGINAL

M:\DOS\WPFILES\MAXALT.LBL

MEMO

To: Division Files, NDA 20864 and NDA 20865 (Maxalt Tablets and Rapidisc)
From: Thomas D. Steele, Ph.D /S/
Subject: Sponsor's Labeling Revisions (May 14, 1998)
Date: May 20, 1998

The pharmacologist's comments to the May 14, 1998 labeling revisions are provided.

1 Page(s) Redacted

DRAFT LABELING

Original NDAs 20864, 20865
cc: /Division Files, HFD-120
/GFitzgerald, Ph.D., HFD-120 /S/ 5/22/98
/RLevin, M.D., HFD-120
/AOliva, M.D., HFD-120
/LChen, R.Ph., HFD-120
/TSteele, Ph.D., HFD-120

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Original Summary

NDA No.: 20864 **Submission Date:** 6/30/97
Review Date: 4/20/98

Drug: MAXALT™ (rizatriptan benzoate) Tablets (5 and 10 mg)

Sponsor: Merck & Co.
P.O. Box 4, BLA-20
West Point, PA 19486

Reviewer: T.D. Steele

Indication: acute treatment of migraine attacks with and without aura

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

Related INDs, NDAs: IND NDA 20865

Chemical Information:

CAS Number: 145202308-66-0

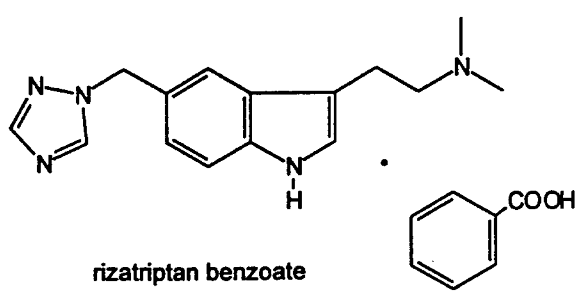
IUPAC Name: N,N-Dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate

Other Names: MK-0462; L-705,126-004B

Empirical Formula: $C_{15}H_{19}N_5O_5 . C_7H_6O_2$

Molecular Weight: 391.47

Structure:



rizatriptan benzoate

Note: Portions of this review were excerpted directly from the sponsor's submission.

Review Outline

A. PHARMACOLOGY

An extensive non-clinical pharmacology program characterized the pharmacodynamic properties of RIZ and some of its metabolites. RIZ was shown to be a relatively selective, fully efficacious 5-$HT_{1B/1D}$ agonist with no significant activity at non-serotonergic receptors. RIZ appears to be more potent in contracting vasculature thought to be important in the genesis of migraine (e.g. meningeal artery) as compared to vasculature associated with important side effects (e.g.. coronary artery). The antimigraine potential of RIZ was demonstrated in studies of carotid blood flow in dogs and ferrets, and in the neurogenic dural plasma extravasation model.

A.1 Mechanism of Action

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ON ORIGINAL

The binding activity of RIZ and some metabolites at cloned or brain 5-HT receptors is shown in sponsor Table F-1. It is noted that some of the nomenclature and subtype identifications have changed over the course of the past several years, which confuses some of the descriptions of the drug's receptor activity. Based on the cloned human receptor data, RIZ can be described as selective for the 5-HT_{1D} and 5-HT_{1B} subtypes, which were formerly known as the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. The binding activity of RIZ at rat cortical 5-HT_{1B} receptors is markedly lower than at human receptors. This difference is due to a single amino acid change in the binding domain that confers distinct pharmacological properties. Thus, the description of the binding activity of RIZ will be based on its binding profile at cloned human receptors.

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.

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2. **Binding Selectivity of the Human Urinary Metabolites of Rizatriptan at Human, Pig and Rat Brain 5-HT Receptors**

Table F-1. Radioligand Binding Activity of Rizatriptan and its Minor Monodesmethyl and Major Indole Acetic Acid Metabolites at Human and Animal 5-HT Receptors In Vitro

Receptor	Source	Animal Receptors (IC_{50} nM)			Human Receptors (IC_{50} nM)		
		Rizatriptan (Parent)	L-706,248 (Minor)	L-749,335 (Major)	Rizatriptan (Parent)	L-706,248 (Minor)	L-749,335 (Major)
5-HT_{1D}	Human cloned	N/A	N/A	N/A	11	9	>10,000
5-HT_{1B}	Human cloned	N/A	N/A	N/A	41	19	>10,000
5-$HT_{1B/1D}$	Pig/human cortex	16	6.5	>10,000	12	6	>10,000
5-HT_{1B}	Rat cortex	1600	220	>10,000	N/A	N/A	N/A
5-HT_{1A}	Pig/human cortex	320	330	>10,000	450	310	>10,000
5-HT_{1E}	Human cloned	N/A	N/A	N/A	170	210	>10,000
5-HT_{2A}	Rat/human cortex	7200	3500	>10,000	5900	6,900	>10,000
5-HT_{2C}	Pig/human cortex	7300	6000	>10,000	>10,000	>10,000	>10,000
5-HT_3	Rat/human cortex	4100	7700	>10,000	>10,000	9,400	10,000

N/A Not Applicable.
Binding results are given as IC_{50} values (the concentration required to inhibit specific binding by 50%). All experiments were carried out with a radioligand concentration which is close to its K_d and hence IC_{50} values approximate K_i.

[Refs. F–1; F–2]

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RIZ showed modest affinity at the 5-HT_{1F} (IC_{50} = 230 nM) and 5-HT_7 (Ki = 430 nM) subtypes, but negligible activity at the 5-HT_{5A} and 5-HT_6 subtypes.

Biochemical studies demonstrated that RIZ is a full agonist at 5-HT_{1B} and 5-HT_{1D} receptors (sponsor Table F-2). Interestingly, RIZ was 10-fold less potent at 5-HT_{1B} vs 5-HT_{1D} receptors in the functional assay, which was greater than the apparent difference in affinity at the two subtypes (i.e., four-fold). This inconsistency is attributed to the mixed affinity states of the human 5-HT_{1B} receptor.

Binding and Functional Activity at Human, Rat, and Dog Cloned 5-HT_{1B} and 5-HT_{1D} Receptors (Cont.)

Table F-2 Radioligand Binding and Functional Activity of Rizatriptan at Human, Dog, and Rat Cloned 5-HT_{1B} and 5-HT_{1D} Receptors In Vitro

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Species	Radioligand Binding		Functional Activity GTPγS			
	5-HT_{1D}	5-HT_{1B}	5-HT_{1D}		5-HT_{1B}	
	IC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)	% 5-HT	EC_{50} (nM)	% 5-HT
Human	11	41	21	95	200	96
Dog	19	17	ND	ND	ND	ND
Rat	12	260	11	105	1700	101

ND=Not determined. Binding results are given as IC_{50} values (the concentration required to inhibit specific binding by 50%). All experiments were carried out with a radioligand concentration which is close to its K_d and hence IC_{50} values approximate K_i. Potencies are given as EC_{50} values (the concentration required to stimulate [^{35}S]GTPγS binding by 50%). Efficacy values are given as a percentage of the maximal 5-HT response.

[Refs. F-2; F-3]

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A.2 Selectivity of Neurochemical Actions

The binding activity of RIZ at 35 other receptor subtypes was assessed in a Novascreen. The only non-serotonergic receptors where ~50% or greater activity was detected were H_1 and M_2 receptors, but the weak displacement observed is not regarded as biologically significant (sponsor Table 3).

A confirmatory study with human brain H_1 and rat brain muscarinic receptors did not reveal significant effects of RIZ at these sites. In a separate study with cloned human adrenergic receptors, RIZ had moderate affinity 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}). Note that significant α_2 receptor activity was not detected in the Novascreen with a non-selective subtype displacing ligand.

The binding profile of the RIZ RAPIDISC degradation product was assessed in a Panlabs screen at 122 sites. The only detectable activity at the choline uptake site (IC_{50} ~10 μM) is not considered biologically significant.

Table 3 Profile receptor selectivity report on L-705,126 from NovaScreen

Receptor/Selectivity	Radioligand	Percent Inhibition (Average; N=2) 10^{-9} M	10^{-7} M	10^{-5} M
Adenosine				
Adenosine 1	[^{3}H]-CPX	7.5	5.7	5.8
Adenosine 2	[^{3}H]-NECA + CPA*	-8.6	-5.5	2.2
Adrenergic				
Alpha 1	[^{3}H]-Prazosin	3.3	0.2	24.7
Alpha 2	[^{3}H]-RX 781094	-5.3	-4.0	38.5
Beta	[^{3}H]-DHA	-6.9	-3.9	-10.1
Amino Acids				
Excitatory				
Quisqualate	[^{3}H]-AMPA	-3.5	18.2	19.7
Kainate	[^{3}H]-Kainic Acid	-6.6	1.3	-2.6
NMDA	[^{3}H]-CGS 19755	-11.7	-9.0	-9.6
PCP	[^{3}H]-TCP	5.4	8.5	0.0
Glycine	[^{3}H]-Glycine	15.4	9.3	10.1
Sigma	[^{3}H]-DTG	5.3	2.0	14.4
Inhibitory				
Glycine	[^{3}H]-Strychnine	18.7	18.6	-10.7
$GABA_A$	[^{3}H]-GABA	-6.6	-3.5	-9.7
$GABA_B$	[^{3}H]-GABA + Isoguvacine*	2.4	6.9	-6.5
Benzodiazepine	[^{3}H]-Flunitrazepam	6.6	-0.2	2.3
Biogenic Amines				
Dopamine 1	[^{3}H]-SCH 23390	4.2	0.7	4.0
Dopamine 2	[^{3}H]-Sulpiride	-0.5	0.7	27.2
Serotonin 1	[^{3}H]-5-HT	-2.8	9.5	**85.8**
Serotonin 2	[^{3}H]-Ketanserin	-0.4	8.7	19.3

Table 3 (Cont.)

Receptor/Selectivity	Radioligand	Percent Inhibition (Average; N=2) 10^{-9} M	10^{-7} M	10^{-5} M
Biogenic Amines				
Histamine 1	[^{3}H]-Pyrilamine	9.7	11.2	47.8
Channel Proteins				
Calcium	[^{125}I]-Omegaconotoxin	-4.6	2.7	3.0
Calcium	[^{3}H]-Nitrepdipine	0.7	1.2	1.9
Chloride	[^{3}H]-TBOB	-7.0	-0.2	-10.3
Potassium	[^{125}I]-Apamin	-0.8	6.3	17.3
Cholinergics				
Muscarinic 1	[^{3}H]-Pirenzepine	8.0	6.3	**78.2**
Muscarinic 2	[^{3}H]-QNB	6.5	3.5	41.7
Nicotinic	[^{3}H]-NMCl	5.6	11.9	1.6
Opiate				
mu	[^{3}H]-DAGO	-2.2	1.8	4.6
delta	[^{3}H]-DPDPEN	3.4	2.7	4.1
kappa	[^{3}H]-U69593	4.7	0.9	-0.3
Prostanoids				
Leukotriene B_4	[^{3}H]-LTB_4	0.4	-4.9	-2.5
Leukotriene D_4	[^{3}H]-LTD_4	5.6	-3.5	-5.2
Thromboxane A_2	[^{3}H]SQ 29548	7.8	5.7	9.5
Second Messenger Systems				
Adenylate Cyclase Forskolin	[^{3}H]-Forskolin	4.9	1.3	3.6
Second Messenger Systems				
Protein Kinase C Phorbol Ester	[^{3}H]-PDBU	-0.7	-4.7	-9.7

Values are expressed as the percent inhibition of specific binding and represent the average of duplicate tubes at each of the concentrations tested. Bolded values represent inhibition of fifty percent or greater (see attached Verification Report). For details of assay descriptions, see attached Assay Protocol Summaries.

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A.3. Functional Studies *In Vitro*

The pharmacodynamic activity of 5-HT_{1D} agonists thought to be important for their antimigraine effects is cerebral vasoconstriction. The effects of RIZ were assessed in various vascular preparations that are abundant in different receptor subtypes to assess its functional selectivity and potency. The most important preparations for the wanted and unwanted vasoconstrictive effects of RIZ are the human middle meningeal artery (antimigraine) and the coronary artery (side effects). RIZ was compared to sumatriptan, and the results were analyzed by a meta-analysis (shown in sponsor Table F-8). The data suggested that RIZ was more efficacious than SUM in contracting middle meningeal arteries (reflected by higher Emax), but less efficacious in the coronary arteries. The potency of RIZ was slightly lower than SUM in both tissues (higher EC_{50}s). This analysis is supportive of the sponsor's conclusion that RIZ may be preferable to sumatriptan with respect to craniovascular:coronary artery selectivity; however, the magnitude of the difference is rather small, and thus of questionable clinical significance. [The stronger effects of 5-HT are likely attributable to 5-HT_2 receptor activation]

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Statistical Meta-Analysis Comparing Effects on Human Isolated Middle Meningeal and Coronary Artery Segments (Cont.)

Table F-8 Summary of the Concentration-Effect Curve Parameters (E_{max} and EC_{50} Values) Derived From Nonlinear Regression Curve Fitting Analysis of Data Obtained for 5-HT, Rizatriptan, and Sumatriptan in Human Isolated Middle Meningeal Artery and Human Isolated Coronary Arteries

Agonist	Parameter	Middle Meningeal Artery (MMA) (Table F-3)	Coronary Artery (CA) Single Agonist Study 1 (Table F-5)	Coronary Artery (CA) Crossover Study Study 2 (Table F-7)	Craniovascular Selectivity Ratio (E_{max} MMA/Mean E_{max} CA in Study 1 and 2)
5-HT	E_{max} (% KCl)	160.6	78.2	102.0	1.8
Rizatriptan	E_{max} (% KCl)	132.6	24.8	22.2	5.6
Sumatriptan	E_{max} (% KCl)	105.3	58.1	43.7	2.1
5-HT	EC_{50} (μM)	0.032	0.3	0.2	N/A
Rizatriptan	EC_{50} (μM)	0.090	0.7	1.0	N/A
Sumatriptan	EC_{50} (μM)	0.071	0.5	0.63	N/A

[Ref. F-5]

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Several other *in vitro* functional studies were conducted to assess functional activation by RIZ of 5-HT_{1A}, 5-HT_{2C}, 5-HT_{2A}, M_1, M_2, M_3, and H_1 receptors. The results were generally consistent with those expected based on the binding studies.

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Receptor	Tissue (endpoint)	Result
5-HT_{1A} vs $_{1B/1D}$	g.p. brain (ad. cyc. inhibition)	7X more active at $_{1B/1D}$ vs $_{1A}$
5-HT_{1A}	hippocampus (depolarization)	very weak agonist
5-HT_{1B}	rat vas deferens (inhibit contraction)	weak agonist (IC_{50} = 8.7μM)
5-HT_2	g.p. brain (PI turnover)	inactive (≤ 10μM)
5-HT_{2c}	g.p. choroid plexus (PI turnover) .	inactive (≤ 100 μM)
5-HT_{2A}	rat tail artery	weak partial agonist
M_1	g.p. sup. cerv. gang.	inactive (≤ 30 μM)
M_2	g.p. atria	"
M_3	g.p. ileum	"
H_1	g.p. ileum	"

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A.4. Functional Studies *In Vivo*

The potential antimigraine efficacy of RIZ was assessed in studies of carotid blood flow in ferrets and dogs, and the neurogenic dural plasma extravasation model. Potential centrally-mediated antimigraine actions were evaluated in anesthetized rats. The dog blood flow and rat central activity studies have labeling implications.

Anesthetized dog studies

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In barbitone-anesthetized dogs, the ED_{50} for carotid vasoconstriction was 54 μg/kg, i.v. ([plasma] = 16 ng/ml). A significant effect on coronary blood flow occurred with much higher doses (300 μg/kg, i.v.; [plasma] = 137 ng/ml) (sponsor Fig.4). The relationship of blood flow changes and circulating plasma levels are shown in sponsor Figs. 6&7. The relationship of resistance and plasma levels is shown in Fig. 8.

Figure 4 **Effects of intravenous L-705,126 on carotid and circumflex blood flow in the anaesthetised dog.**

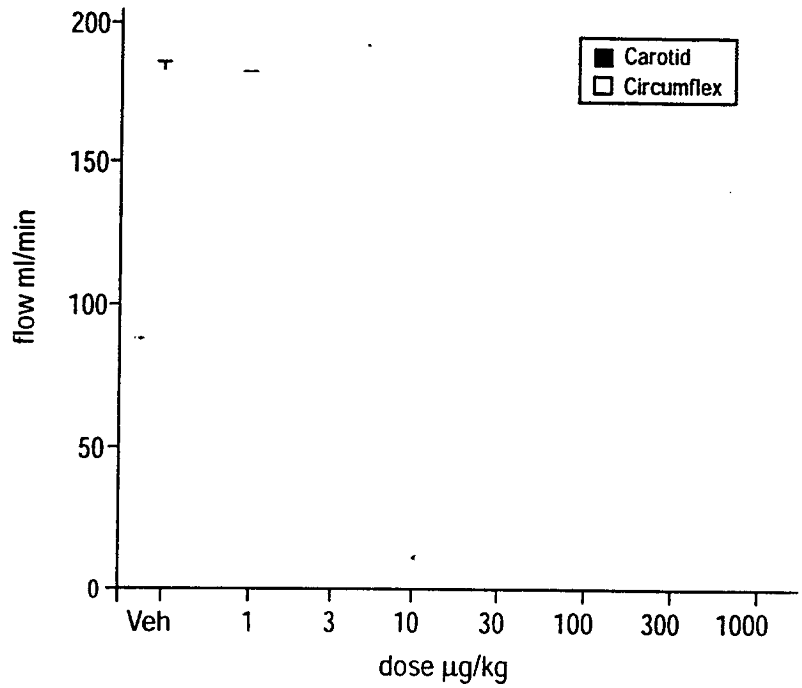

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Figure 6

Relationship between circulating plasma levels of L-705,126 and changes in carotid blood flow following intravenous administration of L-705,126 to anaesthetised dogs.

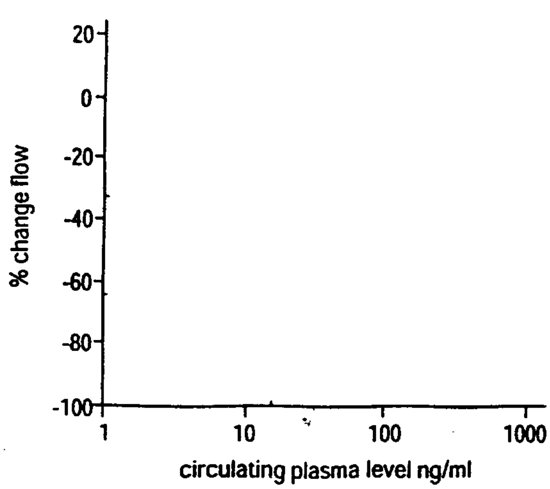


Figure 7

Relationship between circulating plasma levels of L-705,126 and changes in circumflex blood flow following intravenous administration of L-705,126 to anaesthetised dogs.

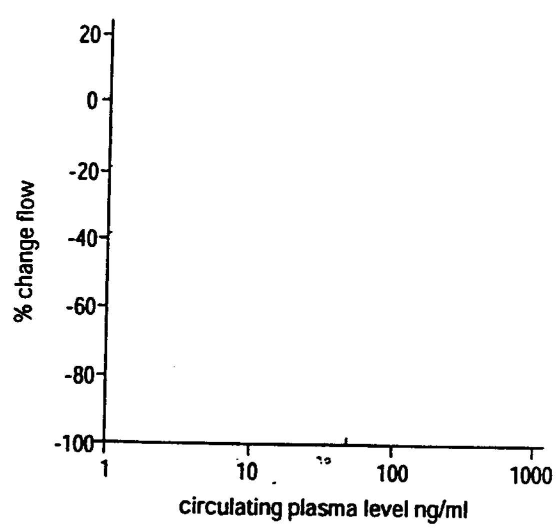
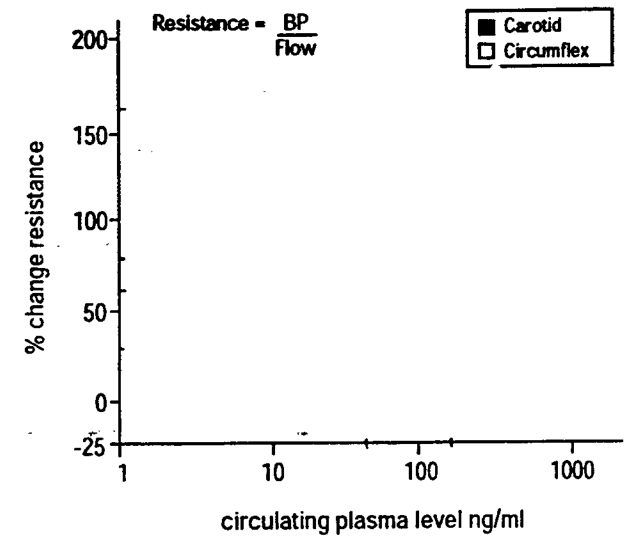


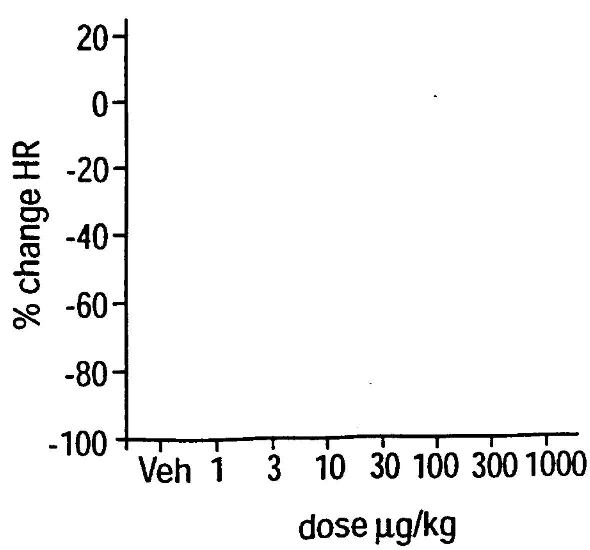
Figure 8 **The relationship between circulating plasma levels of L-705,126 and vascular resistance in the carotid and circumflex artery vascular beds following intravenous administration of L-705,126 to anaesthetised dogs.**

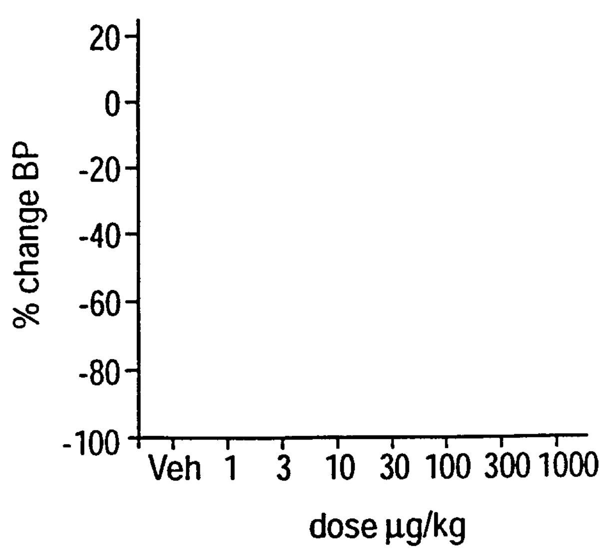


The sponsor suggests that the data demonstrate selectivity of RIZ for the carotid versus the coronary vasculature. The sponsor did not determine an ED_{50} for coronary artery constriction or conduct an appropriate comparative statistical analysis. The interpretation of the graphical data is complicated because of the marked differences in the magnitude of the scale and the absence of a clearly maximal effect. Thus, the actual degree of selectivity is not readily discernible from the data at hand, and any labeling statements regarding this comparison should be carefully worded until a more robust analysis of the data is conducted.

It is noted that RIZ decreased mean arterial pressure and heart rate in the studies at the higher dose levels (sponsor Fig. 3). Therefore, the decrease in coronary flow could be secondary to the decrease in pressure if in fact RIZ is devoid of coronary vasoconstricting activity.

Figure 3 **Effects of intravenous L-705,126 on heart rate and blood pressure in the anaesthetised dog.**





Central Trigeminal Responses to Noxious Dural Stimulation

Electrophysiological studies demonstrated a dose-dependent inhibition of trigeminal neuronal firing in response to noxious stimulation of the dura mater. Effective doses were 1 & 3 mg/kg, i.v. (sponsor Fig. F-7). In a companion study, RIZ was detected in rat brain at a maximum concentration of 260 nM after a 3 mg/kg i.v. dose , but was undetectable after a 3 mg/kg oral dose (LOD = 75 nM).

Based on these findings, the sponsor contends (in labeling) that central actions may contribute to the clinical antimigraine efficacy of RIZ. Pharmacokinetic studies in rats indicate that plasma levels following a 3 mg/kg, i.v., dose are well in excess of expected therapeutic exposures (at least 10-fold) (sponsor Fig. G-3). Thus, central actions probably do not contribute to clinical efficacy of RIZ at therapeutic levels.

Figure F-7

Dose-Dependent Inhibition by Rizatriptan of the Firing of Single Trigeminal Nucleus Caudalis Neurons Responding to Noxious Stimulation of the Dura Mater in the Vicinity of the Middle Meningeal Artery

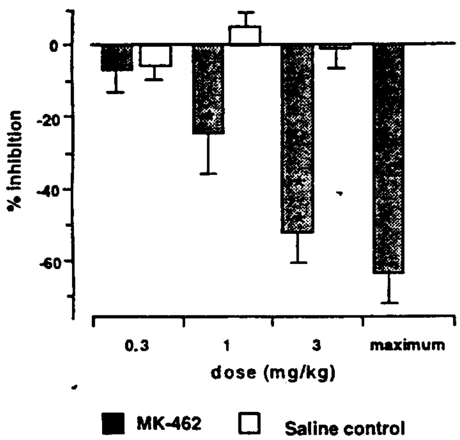
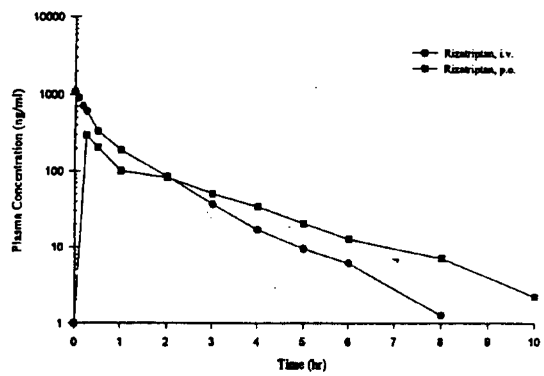


Figure G-3

Mean (n = 4) Plasma Concentrations of Rizatriptan in Rats (3 mg/kg i.v. or p.o.) [Ref. G-1]



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Anesthetized ferret studies

RIZ caused a dose-dependent decrease in carotid blood flow (increased resistance) with an ED_{50} of 20 μg/kg, i.v., in anesthetized ferrets. There was no dimunition of effect with repeated dosing (3 x 15 μg/kg every 45 min).

Rat neurogenic plasma extravasation and vasodilation models

RIZ caused a dose-dependent inhibition of extravasation produced 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).

B. SAFETY PHARMACOLOGY

Cardiovascular safety studies revealed 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. No other noteworthy effects of RIZ on other organ systems were identified.

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B.1. Central Nervous System Effects

Few potential CNS side effects appeared in a modest array of assays. RIZ did not cause noteworthy hypothermic effects or behavioral activation when administered centrally or peripherally at high doses to rats or mice. Mild sedation, hypothermia and transient emesis were evoked in monkeys by a cumulative dosage regimen that produced high plasma levels (1546 ng/ml). Dogs appeared slightly more sensitive to possible CNS-mediated effects; mydriasis, head-shaking and behavioral activation were observed after oral administration of 0.5-2.0 mg/kg RIZ. These data suggest that propensity for RIZ-associated CNS side effects is minimal at clinically relevant doses.

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B.2. Cardiovascular/Respiratory Effects

Triptans may produce cardiovascular effects by direct activation of vascular serotonergic receptors, or by disrupting central reflexes. Some of these effects may be due to activation of receptors other than the 5-HT_{1B} or 5-HT_{1D} subtypes. The sponsor conducted a limited analysis of the cardiovascular and behavioral effects of RIZ in conscious dogs and monkeys, and several studies of reflex interactions. The studies revealed that RIZ has the potential to directly influence the cardiovascular system in dogs and monkeys at high doses, and produces sympatholytic effects similar to other 5-$HT_{1B/1D}$ agonists.

An oral dose of 5 mg/kg RIZ (peak plasma conc = 1642 ng/ml) to two conscious dogs caused marked, sustained increases in blood pressure (~40 mm Hg) and heart rate (~100 bpm; doubling of control level). The lower dose of 1 mg/kg (peak plasm conc = 317 ng/ml) caused mild tachycardia (~30 bpm), but no effect on blood pressure. Repeated dosing with 2 mg/kg (1 every 2 hr for 3 doses) caused moderate, sustained increases in blood pressure and heart rate. The cardiovascular effects were accompanied by behavioral activation and mydriasis.

RIZ administration to two conscious rhesus monkeys in an ascending regimen (0.1, 0.3, and 1.0 mg/kg, i.v., every hour) 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.

The potential central effects of RIZ on CV responses in anesthetized rats were assessed by intracisternal administration of up to 90 nmol. RIZ did not alter blood pressure or heart rate, unlike 5-HT_{1A} agonists which cause hypotension and bradycardia. RIZ also did not evoke the "von Bezold-Jarisch" vagal reflex, which can be evoked by 5-HT_3 receptor activation.

In anesthetized dogs, 0.3 mg/kg RIZ, i.v., caused mild, sustained (up to 60 min) hypotension and transient bradycardia. No changes in respiratory function were observed in another group of dogs that received the same doses. Responses to autonomic challenges (e.g. vagal or ganglionic stimulation, adrenergic or cholinergic agonists) were not consistently affected by RIZ, except for a decrease in the pressor response caused by a muscarinic ganglionic stimulant. The lack of peripheral anti-vagal effects of RIZ (0.1-0.3 mg/kg, i.v.; plasma concentrations of 25 and 123 ng/ml at 5 min post-dose) were confirmed in a more extensive study of β-blocked dogs. These studies suggest that RIZ should not potentiate vagal influences on the heart despite its own mild CV depressant effects.

The potential sympathetic cardiovascular interactions of RIZ were evaluated in pithed rats and guinea pigs. Intravenous administration of RIZ to rats (1-10 mg/kg) and guinea pigs (0.3-3.0 mg/kg) inhibited the pressor response evoked by electrical stimulation of preganglionic sympathetic nerves, but not that evoked by exogenous NE. This finding suggests 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.

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B.3. Gastrointestinal Effects

RIZ reduced basal gastric acid output in 2 of 3 dogs administered 2 mg/kg *via* a gastric fistula, but the mean differences were not significant (acid output [mEq/90 min]: veh = 0.31, RIZ = 0.06). RIZ did not affect gastrin-stimulated acid output.

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B.4. Renal Effects

RIZ (1 mg/kg, p.o.) caused slight, transient increases in average urine flow, and sodium and potassium excretion. Minimal decreases in glomerular filtration rate and Effective Renal Plasma Flow were also observed.

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B.5. Drug Interactions *In Vivo*

The coadministration of amitriptyline (AMI) or fluoxetine (FLX) at clinically relevant plasma concentrations did not alter the effects of RIZ (10-300 μg/kg, i.v.) on carotid or coronary blood flow in anesthetized dogs. Neither drug influenced the plasma concentration of RIZ. In conscious dogs, AMI (1 mg/kg, i.v.) and FLX (2 mg/kg, i.v.) caused modest increases in blood pressure and heart rate, but RIZ did not alter these responses. RIZ also did not alter the cardiovascular responses of anesthetized dogs to propranolol, verapamil or dihydroergotamine.

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C. TOXICOLOGY

C.1. Acute Toxicology

C.1.a. Acute Oral and Intravenous Toxicity Studies in Mice and Rats

(GLP; Reports #: TT-91-2729, 2730, 2731, 2732; Vol. 8)
Conducted by: MRL, West Point, PA Study Dates: 9/4/91 - 9/19/91

Methods:

Animals:	Crl:CD-1 (ICR) BR mice;	7-11 wks old;
	Crl:CD(SD) BR rats;	7 wks;
N:	3/sex/group	
Dosages:	oral: 156, 312, 625, 1250, 2500, 5000 mg/kg (as free base in 1% methylcellulose)	
	iv: 25, 50, 100, 200 mg/kg in H_2O	
Lot:	004B(lot 3)	

Parameters monitored: clinical signs and body wt for 14 days

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Results:

Species	Route	Signs	Mortality
mouse	oral	hypoactivity (≥ 156) convulsions, ↓ resp (≥ 625)	LLD: 625 LD_{50}: 700
	i.v.	hypoactivity, loss of r.r., tremors, convulsions (≥ 100)	LLD: 100 LD_{50}: 89
rat	oral	salivation, ptosis, hypoact (≥ 156) ataxia (≥ 1250) tremors, convulsions, ↓ resp (≥2500)	LLD: 2500 LD_{50}: 2227
	i.v.	hypoactivity, ataxia, convulsions (≥ 100)	LLD: 100 LD_{50}: 141

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C.2. Subchronic Toxicology Studies

The sponsor's table below outlines the doses and durations of the studies submitted in the application. Several short-term (< 7 week) range-finding studies were conducted in rats, mice, and dogs to determine appropriate doses for the "definitive" 14-week studies As these pilot studies were generally unremarkable, they were not reviewed. Salient points from these studies that impacted on toxicological assessments are discussed in the EVALUATION. The intravenous studies did not reveal any additional toxicological information, and were not reviewed.

(reviewed studies are marked *)

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Study Number [Reference Number]*	Species/Sex	Study Type/Dose (mg/kg)	Route	Duration
TT #91-657-0 [B-1]	Dogs/M,F	Exploratory/2 doses, 10	Oral	2 days
TT #91-657-1 [B-1]	Dogs/M,F	Exploratory/2 doses, 5	Oral	2 days
TT #91-658-0,-1 [B-2]	Rats/M,F	Toxicity/2, 10, 50 (adjusted/1.6, 8, 40)	Oral	18 days
TT #91-660-0 [B-3]	Dogs/M,F	Toxicity/0.2, 1, 5	Oral	18 days
TT #91-122-0 [B-4]	Rats/M,F	Toxicity/0.5, 2, 10	I.V.	15 days
TT #91-123-0 [B-5]	Dogs/M,F	Toxicity/0.05, 0.2, 1	I.V.	16 days
TT #92-097-0 [B-6]	Rats/M,F	Toxicity/5, 25, 125	Oral	14 wks
TT #92-104-0 [B-7]	Dogs/M,F	Toxicity/0.2, 1, 5	Oral	14 wks
TT #93-052-0 [B-8]	Rats/M,F	Range-Finding/25, 125, 250, 500	Oral	7 wks
TT #93-083-0 [B-9]	Rats/M,F	Range-Finding/750, 1000, 1500, 2000	Oral	8 days
TT #93-085-0 [B-10]	Rats/M,F	Range-Finding/500, 1000, 2000	Oral	14 wks
TT #93-086-0 [B-11]	Mice/M,F	Toxicokinetic/25, 125, 250, 500	Oral	5 wks
TT #93-087-0 [B-12]	Mice/M,F	Range-Finding/25, 125, 250, 500	Oral	14 wks
TT #93-111-0 [B-13]	Rats/M,F	Toxicity/10, 50, 250	Oral	27/53 wks
TT #93-112-0 [B-14]	Dogs/M,F	Toxicity/0.2, 1, 5	Oral	27/53 wks

*[ ] See II. References for citations.
I.V. - Intravenous

C.2.a. 14-Week Oral Toxicity Study in Dogs
(GLP; Report #: TT-92-104-0; Vol. 12)
Conducted by: MRL, West Point, PA   Study Dates: 11/5/92 - 2/5/93

Summary:

RIZ was generally well-tolerated when administered to beagle dogs (4/sex/group) at doses of 0.2, 1.0 and 5.0 mg/kg/day for 14 weeks. No treatment-related deaths occurred. The only clinical sign observed was mydriasis in all dosage groups; its incidence and severity increased with dose. A limited number of HD animals experienced transient weight loss and decreased food consumption. No treatment-related effects in clinical pathology tests, ophthalmology (assessed predose), EKG, gross or histopathology were observed. Exposures increased approximately in proportion to dose.

The NOAEL for the study is 1.0 mg/kg/day, based on reduced body weight and food consumption at the HD. Plasma exposures at the NOAEL were approximately equivalent to human exposures at the MRHD (30 mg) based on AUC (160 ng.hr/ml).

Methods:

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Animals:	Beagle dogs; 36-40 wks old; males: 7.6-12.0 kg, females:
N:	4/sex/group
Dosages:	0.2, 1.0, 5.0 mg/kg/day (calculated as free base) [The sponsor did not provide a rationale for dosage selection, but the HD is the same as that used in a preliminary 18-day study]
Route/Regimen:	one daily gavage administration
Vehicle:	H_2O (5 ml/kg)
Lot:	004B007

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Parameters monitored:	clinical signs	-	daily
	body wt	-	weekly
	food cons	-	3-4X weekly
	ophthalmic exam	-	wks 3, 7, 12 (predosing)
	EKG	-	wks 4, 8, 12 (3-8 hrs post-dose)
	hematology*	-	wks 3, 7, 12
	clinical chemistry*	-	wks 3, 7, 12
	urinalysis	-	wks 7, 12
	histopathology*	-	complete on Con & HD
	plasma levels	-	day 1, wk 13 (20 min - 24 hr postdose)

* parameters are identified in an appendix Table

Results:

Mortality: No treatment-related deaths occurred. One LDF was sacrificed during week 10 due to vaginal prolapse that was unresponsive to treatment.

Clin Obs: No data tables of clinical findings were submitted. The sponsor reports in the text that mydriasis occurred in all dosage groups with a dose-related increase in intensity (i.e., slow response to light at LD, partial response to light at MD, complete refractiveness of pupillary constriction at HD). MD and LD animals developed tolerance.

Body Wt/ Food Con: 3/8 HD dogs lost weight (> 0.2 kg) during week 1 and subsequently recovered. Food consumption also tended to be lower in HD dogs during weeks 1 and 2. No treatment-related effects on body weight gain or food consumption were evident at termination.

EKG: The sponsor states that there were no treatment-related effects (no data were provided).

Ophthalm: The sponsor states that there were no treatment-related effects (no data were provided).

The ophthalmological exams were conducted predose; the ophthalmological changes with other "triptans" are generally transient for a period of several hrs post-dosing.

Hematol: No treatment-related effects

Clin Chem: No treatment-related effects

Urinalysis: No treatment-related effects

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Org Wts: No treatment-related effects

Gross Path: No treatment-related effects

Histopath: No treatment-related effects

Toxicokinetics: Increases in exposure were approximately dose proportional. Data were similar at both time points indicating that repeated treatment does not alter drug disposition.

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		0.2		1.0		5.0	
		M	F	M	F	M	F
Cmax (ng/ml)	day 1	19	24	120	144	866	970
	wk 13	24	20	128	143	850	1002
AUC (ng.hr/ml)	day 1	18	22	179	175	1271	1243
	wk 13	18	24	185	160	1169	1219
Tmax (hrs)	day 1	0.75	0.33	0.50	0.33	0.42	0.33
	wk 13	0.42	0.44	0.50	0.33	0.50	0.33

C.2.b. MK-0462: Fourteen-Week Oral Range-Finding Study in Rats
(GLP; Report #: TT 93-085-0; Vols.)13-14
Conducted by: Merck Research Laboratories, West Point, PA — Study Dates: 7/6/93 - 10/5/93

Summary:

Rats (10/sex/group) were administered RIZ by gavage at doses of 500, 1000 and 2000 mg/kg/day for 14 weeks. Several deaths occurred at the MD (1M, 2F) and HD (3M, 5F). No adverse necropsy findings were identified as associated with death; thymic "depletion" or necrosis were the only findings in the decedent animals (2 HDM, 1 HDF). The HD was terminated on day 8. Clinical signs were ptosis, hypoactivity and salivation at all dose levels, and head tremors at the MD beginning in week 5. Body weight gain was markedly reduced at the MD coincident with reduced food consumption. Alkaline phosphatase was increased in MDM ( ) and MDF (but there was no corresponding histopathology finding. Mean liver weights were slightly increased in both LD and MD rats. Plasma levels increased in proportion to dose in F, and slightly greater than proportional in M. Absorption tended to be prolonged at the higher dosage levels.

A NOAEL was not established because of the significant clinical signs at the LD. Plasma exposures at this level exceeded human exposures at the MRHD (30 mg) by approximately 1000-fold based on AUC.

The LD may be considered an MTD in males for a carcinogenicity study based on the 9% reduction in body weight gain. The MTD in females is between 500 and 1000 mg/kg, but cannot be precisely determined from the present data.

Methods:

Animals:	Crl:CD(SD)BR rats; 6 wks old; males: , females
N:	10/sex/group
Dosages:	500, 1000, 2000 mg/kg/day (calculated as the free base) [The dose levels were selected based on previous range-finding studies to extend from the No-Effect range (500 mg/kg) to the lethal range (2000 mg/kg)]
Route/Freq:	one daily gavage administration
Vehicle:	0.5% methylcellulose (10 ml/kg)
Lot:	004B010
Feeding:	rationed; M: 24g, F: 17 g

Parameters monitored:	clinical signs	-	daily
	body wt	-	1-2X weekly
	food cons	-	2X weekly (visual inspection)
	ophthalmic exam	-	wks 6 & 12 (Con & HD)
	hematology*	-	wks 6 & 10
	clinical chemistry*	-	"
	urinalysis	-	"

histopathology*	-	complete on Con & HD
plasma levels	-	LD, MD: wk 4 (20 min - 24 hr postdose) HD: d8 (20 min - 6 hr postdose) (N = 3/timepoint)

* parameters are identified in an appendix Table

Results:

Mortality: 2000 mg/kg - 3/10 M (1 dead d2, 1 dead d5, 1 sac d5) and 5/10 F (3 dead d5, 1 sac d5, 1 dead d8);
1000 mg/kg - 1/10 M (dead wk12) and 2/10 F (1 dead wk 2, 1 dead wk 13)

No necropsy findings were associated with deaths.

Clinical: ptosis, hypoactivity, salivation at all doses; head tremors at 1000 beginning wk 5.

Body Wt: see Sponsor Figs. 1&2

MALES

Dose	Δ b.w.	%Δ b.w.g.
Con	257	-
500	234	9
1000	201	22*

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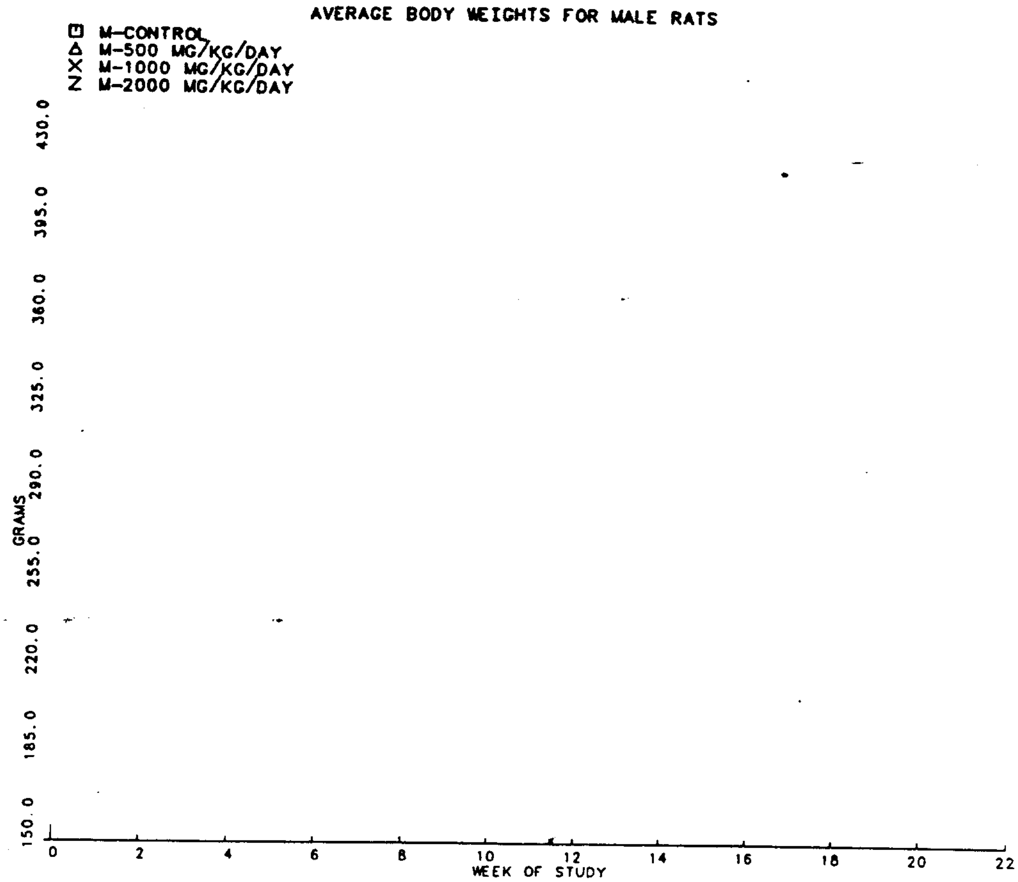
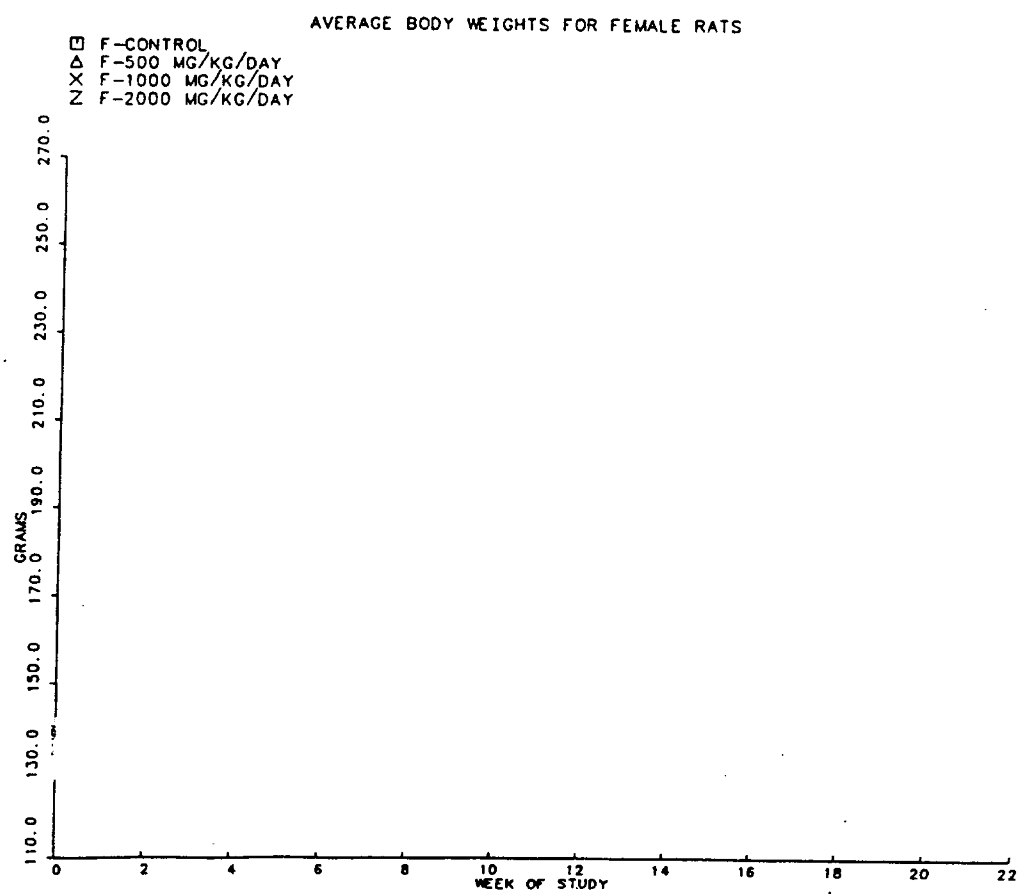
FEMALES

Dose	Δ b.w.	%Δ b.w.g.
Con	105	-
500	106	0
1000	70	33*

* $p < 0.05$ by trend (Tukey)



AVERAGE BODY WEIGHTS FOR MALE RATS
M-CONTROL
M-500 MG/KG/DAY
M-1000 MG/KG/DAY
M-2000 MG/KG/DAY
GRAMS
150.0
185.0
220.0
255.0
290.0
325.0
360.0
395.0
430.0
0
2
4
6
8
10
12
14
16
18
20
22
WEEK OF STUDY



AVERAGE BODY WEIGHTS FOR FEMALE RATS
F-CONTROL
F-500 MG/KG/DAY
F-1000 MG/KG/DAY
F-2000 MG/KG/DAY
GRAMS
110.0
130.0
150.0
170.0
190.0
210.0
230.0
250.0
270.0
0
2
4
6
8
10
12
14
16
18
20
22
WEEK OF STUDY

Food Cons: Data were not provided. Visual inspection suggested decreases in 8/10 MDM and 2/10 MDF.

Ophth: Data were not provided. The sponsor states that there were no treatment-related effects, but no. The timing of the exam with respect to dose was not stated.

Hematol: No treatment-related effects

Clin Chem: ↑ AP (group mean) in 1000M , 1000F

Urinalysis: No treatment-related effects

Organ Wts: No changes were identified by sponsor as treatment-related. Mean increases in liver wts were noted on review (1000M: 18%; 1000F: 32%; 500M: 22%; 500F: 27%).

Gross Path: No treatment-related effects

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Histopath: No treatment-related effects

Toxicokinetics: Plasma levels were determined during week 4 for the LD and MD, and on day 8 in the HD (just prior to termination of this group). Drug absorption was relatively rapid and prolonged; levels were sustained for up to 8 hrs postdosing. Increases were dose proportional in F, and slightly greater than dose proportional in M between the LD and the MD. Saturation was apparent at the HD.

	500		1000		2000	
	M	F	M	F	M	F
Cmax (µg/ml)	22	25	37	50	42	51
AUC (µg.hr/ml)	163	215	525	424		
Tmax (hrs)	1	2	4	4	6	0.3

Plasma exposures at the LD exceeded human exposures by ≥ 1000-fold.

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C.2.c. MK-0462: Fourteen-Week Oral Range-Finding Study in Mice

(GLP; Report #: TT-93-087-0; Vol. 15)
Conducted by: MRL, West Point, PA Study Dates: 7/15/93 - 10/14/93

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Summary:

Mice (10/sex/group) were administered RIZ by gavage at doses of 25, 125, 250 and 500 mg/kg/day (referred to as LLD, LD, MD, HD) for 14 weeks. Two treatment-related deaths occurred in the HD group. The 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 in clinical pathology or histopathology were observed except for slightly increased in erythron at 500 mg/kg. Relative kidney weights were increased by 25% in HDM.

The sponsor considers 25 mg/kg as the NOAEL; this is conservative because the toxicities (↓ body wt gain and food cons) at the 125 mg/kg level were minimal. Plasma exposures at 25 mg/kg (determined in the 5-week TK study that follows) exceeded human exposures at the MRHD (30 mg) by approximately 44 times based on AUC.

The MTD was 250 mg/kg due to deaths at 500 mg/kg in this study and the 5-week toxicokinetic study.

Methods:

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Animals:	Crl:CD-1(ICR)BR mouses; 40 days old; males: females:
N:	10/sex/group
Dosages:	25, 125, 250, 500 mg/kg/day (calculated as the free base; abbrev: LLD, LD, MD, HD) [The rational for dose selection was not presented]
Route/Freq:	one daily gavage administration
Vehicle:	0.5% methylcellulose (10 ml/kg)
Lot:	004B009
Feeding:	*ad lib*

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Parameters monitored:	clinical signs	-	daily
	body wt	-	1-2X weekly
	food cons	-	2X weekly
	ophthalmic exam	-	wks 5 & 11 (Con & HD)
	hematology*	-	wk 14
	clinical chemistry*	-	"
	histopathology*	-	complete on Con & HD (usually only 5-6/group)

* parameters are identified in an appendix Table

Results:

Mortality: 1 HDM (wk 2) & 1 HDF (wk 6); necropsy finding was GI distension

Clinical: slight hypoactivity (mainly at HD during week 1)

Body Wt: see Sponsor Figs. 1&2

MALES

Dose	Δ b.w.	%Δ b.w.g.
Con	9.8	-
25	10.0	-
125	9.4	4*
250	8.6	12*
500	7.5	29*

FEMALES

Dose	Δ b.w.	%Δ b.w.g.
Con	7.8	-
25	7.8	0
125	7.5	4*
250	6.3	19*
500	6.8	13*

* $p < 0.05$ by trend (Tukey)

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Food Cons: decreased at ≥ 125 mg/kg during week 1; exceeded Con by study end.

Ophth: No data were provided. The sponsor states that there were no treatment-related effects. Unilateral cataracts in 1 HDF, 1 MDF, and 1 LDM late in the study were considered incidental because of low incidence, lack of progression, and unilaterality.

Hematol: 7-10% ↑ in erythroid parameters in HDM and HDF (not toxicologically significant).

Clin Chem: One HDM had ↑ AST, ALT and BUN; no corresponding histopath finding.

Organ Wts: No changes were identified by sponsor as treatment-related. A mean 25% increase of relative kidney wts in HDM was noted on review.

Gross Path: No treatment-related effects

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Histopath: No treatment-related effects (6 ConF, 8 HDF, all ConM and HDM were necropsied).