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20-864/S-002

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NDA 20-864/SE8-002

MAXALT Tablets

(rizatriptan benzoate)

CATEGORY: 1S

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REC.
6/24/02

&

NDA 20-865/SE8-004

MAXALT-MLT

(orally disintegrating tablets)

CATEGORY: 3S

Merck

APPROVAL PACKAGE

Volume 1

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NDA 20-864/SE8-002 Maxalt Tablets
NDA 20-865/SE8-004 Maxalt-MLT
Adolescent Supplement

Approval Package: Volume #1

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JUN 21 2000

NDA 20-864/S-002
NDA 20-865/S-004

Merck & Co., Inc.
P.O. Box 4, BLA-20
Attention: Dennis Erb, Ph.D.
West Point, PA 19486

Dear Dr. Erb:

Please refer to your supplemental new drug applications dated October 26, 1999, received October 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Maxalt Tablets and Maxalt-MLT.

We acknowledge receipt of your submissions dated May 5, 2000 and June 9, 2000.

These supplemental new drug applications provide for the use of Maxalt Tablets and Maxalt-MLT in adolescent migraineurs.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. We also request that you submit the labeling electronically as described in our guidance "Providing Regulatory Submissions in electronic format-NDA." For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-864/S-002, 20-865/S-004" Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-864/S-002
NDA 20-865/S-004

HFD-120/Div. Files
HFD-120/L.Chen
HFD-120/Katz/Feeney/Oliva AP 6/8/00 AP 6/13/00 AP 6/21/00
HFD-710/Jin/R. Chen JJ 6/7/00 YWC 6/7/2000
HFD-860/Baweja

HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - ONLY for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

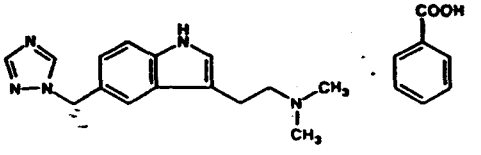
Drafted by: lyc/May 31, 2000
Initialed by:
final: LLC 6/21/00
filename: [illegible] doc
up – 101. doc
APPROVAL (AP)'s ~~ents)~~ LLC 6/21/00

MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT™
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

MAXALT* contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

MAXALT Tablets and MAXALT-MLT** Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. Rizatriptan has weak affinity for other 5-HT$_1$ receptor subtypes (5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$) and the 5-HT$_7$ receptor, but has no significant activity at 5-HT$_2$, 5-HT$_3$, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel

* Registered trademark of MERCK & CO., Inc.
** Trademark of MERCK & CO., Inc.

constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets, but the rate of absorption is somewhat slower with MAXALT-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-$HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-$HT_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

Elderly: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients, (creatinine clearance < 2 mL/min/1.73 m^2), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions (See also PRECAUTIONS, *Drug Interactions.*)

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when MAXALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions.*)

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS; DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of MAXALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Clinical Studies

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 1.

Table 1
Response Rates 2 Hours Following Treatment of Initial Headache

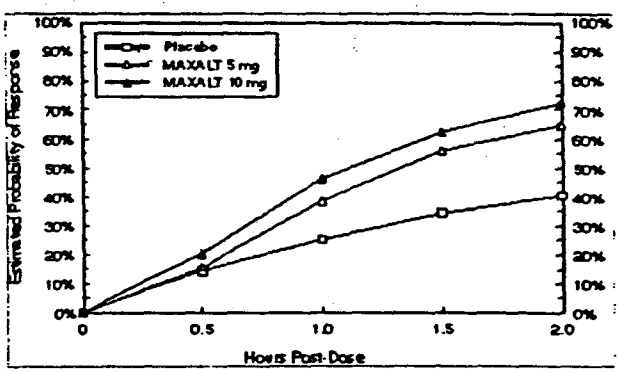
Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours††

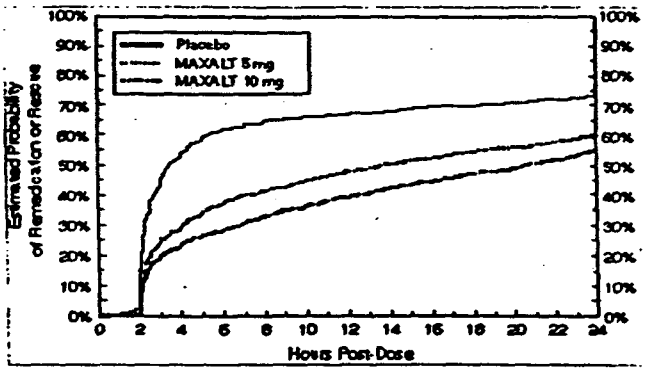


†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment†††



††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

In a single study in adolescents (n=291), there were no statistically significant differences between treatment groups. The headache response rates at 2 hours were 66% and 56% for MAXALT 5 mg Tablets and placebo, respectively.

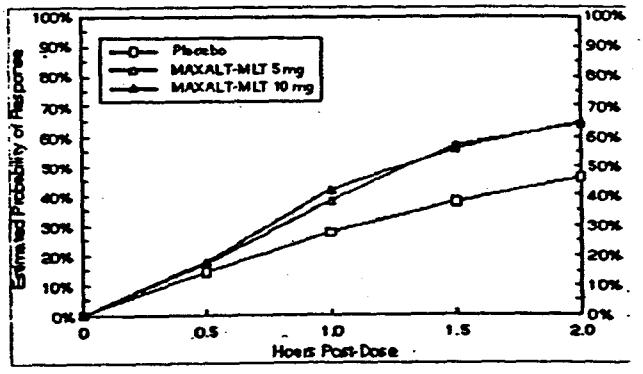
MAXALT-MLT Orally Disintegrating Tablets

The efficacy of MAXALT-MLT 5 mg and 10 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT-MLT were approximately 66% in either the MAXALT-MLT 5 mg and 10 mg groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT-MLT is depicted in Figure 3.

Figure 3: Estimated Probability of Achieving an Initial Headache Response with MAXALT-MLT by 2 Hours‡

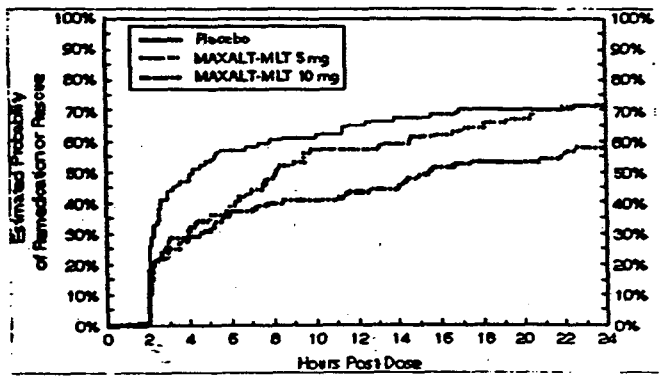


‡ Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 4.

Figure 4: Estimated Probability of Patients Taking a Second Dose of MAXALT-MLT or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment‡‡



‡‡ In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

INDICATIONS AND USAGE

MAXALT is indicated for the acute treatment of migraine attacks with or without aura in adults.

MAXALT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of MAXALT has not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

MAXALT should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because MAXALT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

MAXALT should not be used within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

MAXALT is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

WARNINGS

MAXALT should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: **Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, rizatriptan should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received rizatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of MAXALT and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use MAXALT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to rizatriptan.

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. Among the 3700 patients with migraine who participated in premarketing clinical trials of MAXALT, one patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Cerebrovascular Events and Fatalities Associated with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with MAXALT in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischemic ECG changes in clinical trials (one patient experienced chest pain with possible ischemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see CLINICAL PHARMACOLOGY, *Special Populations*).

Renally Impaired Patients: Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan (see CLINICAL PHARMACOLOGY, *Special Populations*).

Hepatically Impaired Patients: Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see CLINICAL PHARMACOLOGY, *Special Populations*).

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT-MLT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 5-mg orally disintegrating tablet contains 1.05 mg phenylalanine, and each 10-mg orally disintegrating tablet contains 2.10 mg phenylalanine.

Information for Patients

Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness has also been reported in some patients receiving MAXALT. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of MAXALT.

Physicians should instruct their patients to read the patient package insert before taking MAXALT. See the accompanying PATIENT INFORMATION leaflet.

MAXALT-MLT Orally Disintegrating Tablets

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT.

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions.*)

Propranolol: Rizatriptan 5 mg should be used in patients taking propranolol, as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70% (see CLINICAL PHARMACOLOGY, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Other 5-HT$_1$ agonists: The administration of rizatriptan with other 5-HT$_1$ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT$_1$ agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with rizatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. No clinical or pharmacokinetic interactions were observed when MAXALT 10 mg was administered with paroxetine.

Monoamine oxidase inhibitors: Rizatriptan should not be administered to patients taking MAO-A inhibitors and non-selective MAO inhibitors; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of rizatriptan and its metabolite (see CLINICAL PHARMACOLOGY, *Drug Interactions*; CONTRAINDICATIONS).

Drug/Laboratory Test Interactions

MAXALT is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The lifetime carcinogenic potential of rizatriptan was evaluated in a 100-week study in mice and a 106-week study in rats at oral gavage doses of up to 125 mg/kg/day. Exposure data were not obtained in those studies, but plasma AUC's of parent drug measured in other studies after 5 and 21 weeks of oral dosing in mice and rats, respectively, indicate that the exposures to parent drug at the highest dose level in the carcinogenicity studies would have been approximately 150 times (mice) and 240 times (rats) average AUC's measured in humans after three 10 mg doses, the maximum recommended total daily dose. There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis: Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, the *in vitro* mammalian cell mutagenesis assay in V-79 Chinese hamster lung cells, the *in vitro* alkaline elution assay in rat hepatocytes, the *in vitro* chromosomal

aberration assay in Chinese hamster ovary cells and the *in vivo* chromosomal aberration assay in mouse bone marrow.

Impairment of Fertility: In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 225 times the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

Pregnancy: Pregnancy Category C

. In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation with doses of 10 and 100 mg/kg/day. Maternal plasma drug exposures (AUC) at these doses were approximately 15 and 225 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The effects on offspring growth occurred in the absence of any apparent maternal toxicity in this study. The developmental no-effect dose was 2 mg/kg/day (maternal exposure approximately 1.5 times human exposure at the MRDD). The full spectrum of developmental toxicity is not known because adequately high doses, i.e., those producing some maternal toxicity, were not evaluated in the reproduction study. When higher, maternally toxic doses (250 mg/kg/day or greater) were evaluated over the same period of development in a rat dose range-finding study, pup mortality was increased.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses of 100 and 50 mg/kg/day, respectively, during organogenesis. Fetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses (maternal exposures approximately 225 and 115 times the human exposure at the MRDD in rats and rabbits, respectively). The developmental no-effect dose in these studies was 10 mg/kg/day in both rats and rabbits (maternal exposures approximately 15 times human exposure at the MRDD). Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to MAXALT while pregnant. Healthcare providers are encouraged to report any prenatal exposure to MAXALT by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

It is not known whether this drug 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. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatric Use

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, MAXALT is not recommended for use in patients under 18 years of age.

The efficacy of MAXALT Tablets (5 mg) in patients aged 12 to 17 years was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see *Clinical Studies*). Adverse events observed were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long-term safety of rizatriptan in pediatric patients has not been studied.

Use in the Elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with MAXALT is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n=17).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT Tablets. The most common adverse events during treatment with MAXALT were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Table 2 lists the adverse events regardless of drug relationship (incidence ≥ 2% and greater than placebo) after a single dose of MAXALT. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2
Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences
After a Single Dose of MAXALT Tablets or Placebo

	% of Patients		
Adverse Experiences	MAXALT 5 mg (N=977)	MAXALT 10 mg (N=1167)	Placebo (N=627)
Atypical Sensations	4	5	4
Paresthesia	3	4	<2
Pain and other Pressure Sensations	6	9	3
Chest Pain: tightness/pressure and/or heaviness	<2	3	1
Neck/throat/jaw: pain/tightness/pressure	<2	2	1
Regional Pain: tightness/pressure/heaviness	<1	2	0
Pain, location unspecified	3	3	<2
Digestive	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
Neurological	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4
Other			
Asthenia/fatigue	4	7	2

MAXALT was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by

concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of MAXALT: In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT (N=3716) and reported an event divided by the total number of patients exposed to MAXALT. All reported events are included, except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least (>)1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

General: Infrequent were chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. Rare were fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: Frequent were warm/cold sensations.

Cardiovascular: Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare was angina pectoris.

Digestive: Frequent were diarrhea and vomiting. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: Infrequent was dehydration.

Musculoskeletal: Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: Frequent were hypesthesia, mental acuity decreased, euphoria and tremor. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. Rare were: dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: Frequent was dyspnea. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose. epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: Frequent was flushing. Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital system: Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

The adverse experience profile seen with MAXALT-MLT Orally Disintegrating Tablets was similar to that seen with MAXALT Tablets.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of MAXALT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

No overdoses of MAXALT were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5 and 10 mg of MAXALT Tablets or MAXALT-MLT were effective for the acute treatment of migraines in adults. There is evidence that the 10-mg dose may provide a greater effect than the 5-mg dose (see *Clinical Studies*). Individuals may vary in response to doses of MAXALT Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10-mg dose with the potential risk for increased adverse events.

Redosing: Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Patients receiving propranolol: In patients receiving propranolol, the 5-mg dose of MAXALT should be used, up to a maximum of 3 doses in any 24-hour period. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.)

For MAXALT-MLT Orally Disintegrating Tablets, administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

HOW SUPPLIED

No. 3732 — MAXALT Tablets, 5 mg, are pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other. They are supplied as follows:

NDC 0006-0266-06, unit of use carrying case of 6 tablets.

No. 3733 — MAXALT Tablets, 10 mg, are pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other. They are supplied as follows:

NDC 0006-0267-06, unit of use carrying case of 6 tablets.

No. 3800 — MAXALT-MLT Orally Disintegrating Tablets, 5 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified triangle on one side, and measuring 10.0-11.5 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3800-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

No. 3801 — MAXALT-MLT Orally Disintegrating Tablets, 10 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side, and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3801-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

Storage

Store MAXALT Tablets at room temperature, 15-30°C (59-86°F). Dispense in a tight container, if product is subdivided.

Store MAXALT-MLT Orally Disintegrating Tablets at room temperature, 15-30°C (59-86°F). The patient should be instructed not to remove the blister from the outer aluminum pouch until the patient is ready to consume the orally disintegrating tablet inside.

MAXALT Tablets are manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

By:
MSD, Ltd. Cramlington
Northumberland, NE23 9JU, UK

MAXALT-MLT Orally Disintegrating Tablets are manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

By:
Scherer DDS, Ltd.
Swindon, Wiltshire, SN5 8RU, UK

Issued ~~October 1998~~
Printed in USA

TELECOPIER MESSAGE

Merck Research Laboratories
P.O. Box 4
West Point, PA 19486-0004

Number of Pages Including Cover Sheet: 13

Date: 6-12-00

To: Lana Chen
Phone: 301-594-5529
Fax: 301-594-2859

From: Dr. Charlene Sanders
Regulatory Affairs – Domestic
Phone: 610-397-2850
Fax: 610-397-2516

If you have not received the complete fax, please contact Sharon Stukowski at (610) 397-3079.

Regulatory Affairs

P.O. Box 4, BLA-20
West Point PA 19486-0004
Tel 610 397 2850
Fax 610 397 2516

MERCK

June 9, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
HFD-120, Room 4049
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

NDA 20-864/S-002: MAXALT™ Tablets
(rizatriptan benzoate)

NDA 20-865/S-004: MAXALT-MLT™ Orally Disintegrating Tablets
(rizatriptan benzoate)

GENERAL CORRESPONDENCE

Reference is made to the above Adolescent supplement for proposed product labeling. Reference is also made to a fax communication of May 25, 2000 from the FDA about the labeling changes and the follow-up telephone conversation between Ms. Lana Chen, Project Manager, FDA and Charlene Sanders, MD, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on May 25, 2000, regarding the Agency's comments.

The Agency's comments for proposed labeling changes for adolescent migraines have been incorporated into the label. With this letter, we are submitting in hard copy, a draft of the revised section of the label that incorporates the recommendations provided in the May 25, 2000 facsimile. There have not been any other changes to the label other than those indicated. The complete updated labeling package will be submitted in electronic format on or before June 20, 2000.

We are simultaneously submitting this information to NDA 20-864 MAXALT™ Tablets, since there is a single label for both the oral tablet and orally disintegrating tablet.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct any questions or need for additional information to Charlene G. Sanders, M.D. (610-397-2850) or, in my absence, to Dennis M. Erb, Ph.D. (610-397-7597).

Sincerely,

Charlene G. Sanders, M.D.
Director, Regulatory Affairs

Attachment 1

Federal Express #1

Desk Copy: Ms. Lana Chen, HFD-120, Room 4031
Federal Express #2

Q:\Howley\Cyle\MAXALT\20865\General\CorAdlabel060900.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck Research Laboratories, a Division of Merck & Co., Inc.	09-JUN-2000
TELEPHONE NO. *(Include Area Code)* (610) 397-2850	**FACSIMILE (FAX) Number** *(Include Area Code)* (610) 397-2516
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* Sumneytown Pike, P.O. Box 4, BL A-20 West Point, PA 19486	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Charlene G. Sanders, M.D. Director, Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-864

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
rizatriptan benzoate	MAXALT™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
N,N-Dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate	MK-0462

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	5 mg, 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
The acute treatment of migraine attacks with or without aura.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION GENERAL CORRESPONDENCE

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Merck & Co., Inc.:

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* GENERAL CORRESPONDENCE

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Charlene G Sanders, MD	Charlene G. Sanders, M.D. Director, Regulatory Affairs	09-JUN-2000

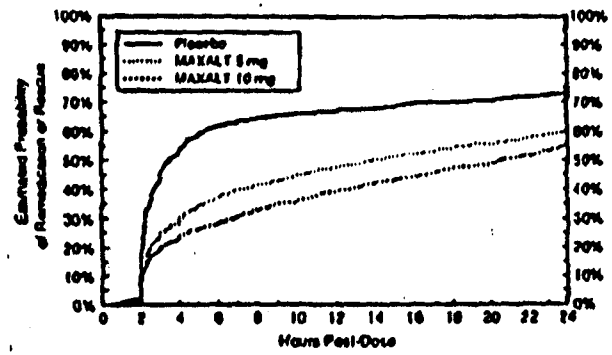
ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Sumneytown Pike, P.O. Box 4, BL A-20 West Point, PA 19486	(610) 397-2850

TEXT SUBMITTED ON 5/5/00 WITH ADDITIONAL REVISIONS

COMMENTS/SUPPORT

MAXALT® (Rizatriptan Benzoate) Tablets
MAXALT-MLT™ (Rizatriptan Benzoate) Orally Disintegrating Tablets

9122102



††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

In a single study in adolescents (n=291), there were no statistically significant differences between treatment groups. The headache response rates at 2 hours were 66% and 56% for MAXALT 5 mg Tablets and placebo, respectively.

Revised per fax from FDA dated 5/25/00.

The efficacy of MAXALT-MLT 5 mg and 10 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT-MLT were approximately 66% in either the MAXALT-MLT 5 mg and 10 mg groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT-MLT is depicted in Figure 3.

NDA 20-864/S-002: May 5, 2000

MAXALT-MLT™
Orally Disinigrating Tablets
(rizatriptan benzoate)

Amendment to Supplemental New Drug Application

Tel 610 397 7597
215 652 5000
Fax 610 397 2516

May 5, 2000

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20850

NDA 20-864/S-002: MAXALT™ Tablets
(rizatriptan benzoate)

Amendment to Supplemental New Drug Application

Reference is made to the supplemental New Drug Application (sNDA) cited above for MAXALT™ Tablets submitted as an electronic archive on October 26, 1999. Reference is also made to a fax from Ms. Lana Chen, Food and Drug Administration, to Dr. Dennis M. Erb, Merck Research Laboratories, a Division of Merck & Co., Inc., on March 8, 2000. In this fax, Ms. Chen provided proposed labeling revisions for the Pediatric Use section of the sNDA. Reference is also made to a telephone conversation between Ms. Lana Chen and Dr. Dennis M. Erb on March 28, 2000 whereby agreement was made to delete the Adolescent Pharmacokinetics statement in the Special Populations section of the label.

As indicated on the attached Form FDA 356h, this amendment provides for changes in the Labeling Section of the approved New Drug Application for MAXALT™ Tablets. All information is in an electronic format as indicated in the Table of Contents for this amendment to Supplement 002.

This amendment provides for revisions to the circular under the Pediatric Use and Special Populations sections. Proposed revisions to the Pediatric Use section include the addition of a statement pertaining to postmarketing adverse experience reports with other triptans as well as a statement with regard to the absence of long term safety information for rizatriptan. Additionally, the sentence pertaining to Adolescent Pharmacokinetics in the Special Populations section has been deleted.

We are simultaneously submitting an amendment to labeling supplement S-004 to NDA 20-865 MAXALT-MLT™ Orally Disintegrating Tablets, since there is a single label for both the oral tablet and orally disintegrating tablet.

All information is in an electronic format as indicated in the Table of Contents for this supplemental application. This supplemental application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This supplemental application is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the supplemental application. All documents requiring signatures for certification are included as paper for archival purposes.

Attached electronically (CD) in draft for the Agency's review and approval are the following items:

Labeling
II. Labeling text
   a. Proposed labeling text
      (#9122102)

Summary
I. Annotated Package Circular

The Microsoft WORD version of the proposed labeling text is also provided on a separate diskette/CD.

All of the information is contained on one CD and has an approximate size of 100MB. We have taken precautions to insure that any software on the CD is free of computer viruses (Norton Anti-Virus 4.0. Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Neuropharmacological Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Lana Chen. Regulatory Project Manager, Division of Neuropharmacological Drug Products. MRL will follow-up with Ms. Chen to ensure that the appropriate reviewers have been given access to this electronic submission.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information concerning this supplemental application, please contact Dennis M. Erb, Ph.D. (610-397-7597) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.
Senior Director
Regulatory Affairs

Attachments: CD

Federal Express #1

Desk Copies: Russell G. Katz, M.D., Director (cover letter)
HFD-120, Room 4049
Federal Express #2

Ms. Lana Chen, Regulatory Project Manager
(cover letter and diskette containing WORD version
of the proposed text as a review aid)
HFD-120, Room 4031
Federal Express #2

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FOOD AND DRUG ADMINISTRATION

See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code Of Federal Regulations, 314)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck & Co., Inc.	05 NOV 00
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(610) 397-7597	(610) 397-2516

APPLICANT ADDRESS *(Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued):*

P O Box 4
BLA-20
West Point, PA 19486-0004

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

Dennis M. Erb, Ph.D.
Senior Director, Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-864

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Rizatriptan benzoate	MAXALT™

CHEMICAL/ BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* N,N-Dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate

CODE NAME *(If any)* MK-0462

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION
Tablets	5 mg 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
The acute treatment of migraine attacks with or without aura.

APPLICATION INFORMATION

APPLICATION TYPE *(Check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCED LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for the drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Merck & Co., Inc.:

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Instructions on Reverse Side Before Completing This Form

APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-10
P. O. Box 4
West Point, PA 19486

3. PRODUCT NAME

MAXALT® TABLETS (RIZATRIPTAN BENZOATE)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- ☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION
- ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA)

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 397-2383

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

N020864

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- ☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*
- ☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*
- ☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*
- ☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*
- ☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

- ☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- ☐ A CRUDE ALLERGENIC EXTRACT PRODUCT
- ☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- ☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
- ☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please DO NOT RETURN this form to this address.

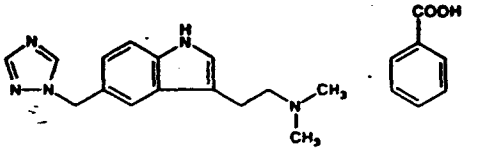
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Bonnie J. Goldmann	Bonnie J. Goldmann, M.D. Vice President, Domestic Liaison Regulatory Affairs	05MAY00

MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT™
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

MAXALT contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. Rizatriptan has weak affinity for other 5-HT$_1$ receptor subtypes (5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$) and the 5-HT$_7$ receptor, but has no significant activity at 5-HT$_2$, 5-HT$_3$, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel

constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets, but the rate of absorption is somewhat slower with MAXALT-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-$HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-$HT_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

Elderly: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients, (creatinine clearance < 2 mL/min/1.73 m^2), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions (See also PRECAUTIONS, *Drug Interactions.*)

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when MAXALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions.*)

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS; DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of MAXALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Clinical Studies

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 1.

Table 1
Response Rates 2 Hours Following Treatment of Initial Headache

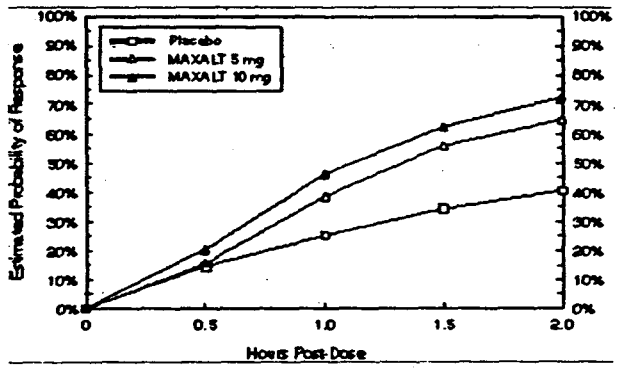
Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours††

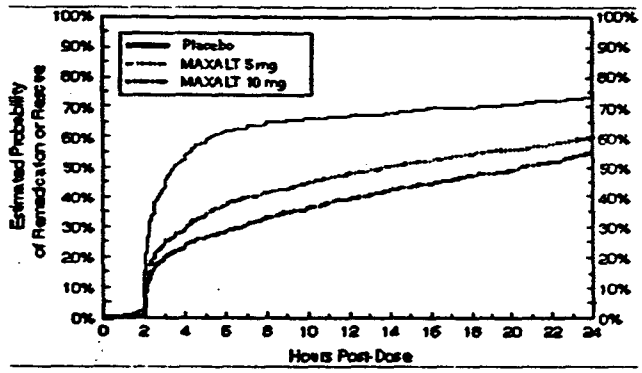


†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment†††



††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

In a single study in adolescents (n=291), 66% of the patients achieved headache relief at 2 hours with MAXALT Tablets 5 mg; this did not differ significantly from placebo (56%).

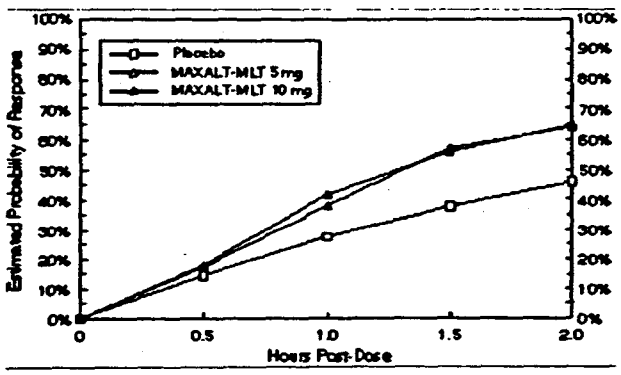
MAXALT-MLT Orally Disintegrating Tablets

The efficacy of MAXALT-MLT 5 mg and 10 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT-MLT were approximately 66% in either the MAXALT-MLT 5 mg and 10 mg groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT-MLT is depicted in Figure 3.

Figure 3: Estimated Probability of Achieving an Initial Headache Response with MAXALT-MLT by 2 Hours‡

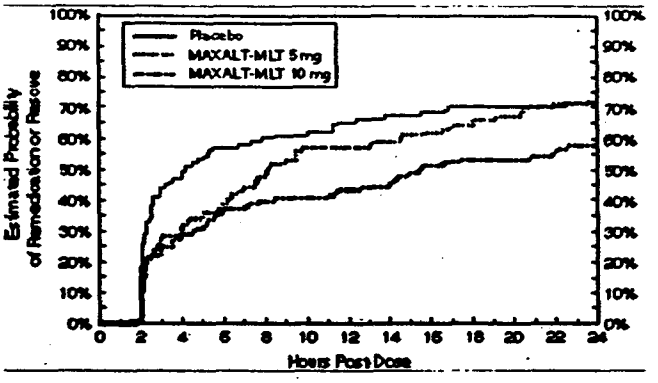


‡ Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 4.

Figure 4: Estimated Probability of Patients Taking a Second Dose of MAXALT-MLT or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment‡‡



‡‡ In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

INDICATIONS AND USAGE

MAXALT is indicated for the acute treatment of migraine attacks with or without aura in adults.

MAXALT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of MAXALT has not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

MAXALT should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because MAXALT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

MAXALT should not be used within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

MAXALT is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

WARNINGS

MAXALT should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: **Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, rizatriptan should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received rizatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of MAXALT and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use MAXALT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to rizatriptan.

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. Among the 3700 patients with migraine who participated in premarketing clinical trials of MAXALT, one patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Cerebrovascular Events and Fatalities Associated with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with MAXALT in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischemic ECG changes in clinical trials (one patient experienced chest pain with possible ischemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see CLINICAL PHARMACOLOGY, *Special Populations*).

Renally Impaired Patients: Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan (see CLINICAL PHARMACOLOGY, *Special Populations*).

Hepatically Impaired Patients: Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see CLINICAL PHARMACOLOGY, *Special Populations*).

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT-MLT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 5-mg orally disintegrating tablet contains 1.05 mg phenylalanine, and each 10-mg orally disintegrating tablet contains 2.10 mg phenylalanine.

Information for Patients

Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness has also been reported in some patients receiving MAXALT. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of MAXALT.

Physicians should instruct their patients to read the patient package insert before taking MAXALT. See the accompanying PATIENT INFORMATION leaflet.

MAXALT-MLT Orally Disintegrating Tablets

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT.

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions*.)

Propranolol: Rizatriptan 5 mg should be used in patients taking propranolol, as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70% (see CLINICAL PHARMACOLOGY, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Other 5-HT$_1$ agonists: The administration of rizatriptan with other 5-HT$_1$ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT$_1$ agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with rizatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. No clinical or pharmacokinetic interactions were observed when MAXALT 10 mg was administered with paroxetine.

Monoamine oxidase inhibitors: Rizatriptan should not be administered to patients taking MAO-A inhibitors and non-selective MAO inhibitors; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of rizatriptan and its metabolite (see CLINICAL PHARMACOLOGY, *Drug Interactions*; CONTRAINDICATIONS).

Drug/Laboratory Test Interactions

MAXALT is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The lifetime carcinogenic potential of rizatriptan was evaluated in a 100-week study in mice and a 106-week study in rats at oral gavage doses of up to 125 mg/kg/day. Exposure data were not obtained in those studies, but plasma AUC's of parent drug measured in other studies after 5 and 21 weeks of oral dosing in mice and rats, respectively, indicate that the exposures to parent drug at the highest dose level in the carcinogenicity studies would have been approximately 150 times (mice) and 240 times (rats) average AUC's measured in humans after three 10 mg doses, the maximum recommended total daily dose. There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis: Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, the *in vitro* mammalian cell mutagenesis assay in V-79 Chinese hamster lung cells, the *in vitro* alkaline elution assay in rat hepatocytes, the *in vitro* chromosomal

aberration assay in Chinese hamster ovary cells and the *in vivo* chromosomal aberration assay in mouse bone marrow.

Impairment of Fertility: In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 225 times the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

Pregnancy: Pregnancy Category C

In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation with doses of 10 and 100 mg/kg/day. Maternal plasma drug exposures (AUC) at these doses were approximately 15 and 225 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The effects on offspring growth occurred in the absence of any apparent maternal toxicity in this study. The developmental no-effect dose was 2 mg/kg/day (maternal exposure approximately 1.5 times human exposure at the MRDD). The full spectrum of developmental toxicity is not known because adequately high doses, i.e., those producing some maternal toxicity, were not evaluated in the reproduction study. When higher, maternally toxic doses (250 mg/kg/day or greater) were evaluated over the same period of development in a rat dose range-finding study, pup mortality was increased.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses of 100 and 50 mg/kg/day, respectively, during organogenesis. Fetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses (maternal exposures approximately 225 and 115 times the human exposure at the MRDD in rats and rabbits, respectively). The developmental no-effect dose in these studies was 10 mg/kg/day in both rats and rabbits (maternal exposures approximately 15 times human exposure at the MRDD). Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to MAXALT while pregnant. Healthcare providers are encouraged to report any prenatal exposure to MAXALT by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

It is not known whether this drug 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. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatric Use

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, MAXALT is not recommended for use in patients under 18 years of age.

The efficacy of MAXALT Tablets (5 mg) in patients aged 12 to 17 years was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see *Clinical Studies*). Adverse events observed were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long-term safety of rizatriptan in pediatric patients has not been studied.

Use in the Elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with MAXALT is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n=17).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT Tablets. The most common adverse events during treatment with MAXALT were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Table 2 lists the adverse events regardless of drug relationship (incidence ≥ 2% and greater than placebo) after a single dose of MAXALT. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2
Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences
After a Single Dose of MAXALT Tablets or Placebo

	% of Patients		
Adverse Experiences	MAXALT 5 mg (N=977)	MAXALT 10 mg (N=1167)	Placebo (N=627)
Atypical Sensations	4	5	4
Paresthesia	3	4	<2
Pain and other Pressure Sensations	6	9	3
Chest Pain: tightness/pressure and/or heaviness	<2	3	1
Neck/throat/jaw: pain/tightness/pressure	<2	2	1
Regional Pain: tightness/pressure/heaviness	<1	2	0
Pain, location unspecified	3	3	<2
Digestive	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
Neurological	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4
Other			
Asthenia/fatigue	4	7	2

MAXALT was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by

concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of MAXALT: In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT (N=3716) and reported an event divided by the total number of patients exposed to MAXALT. All reported events are included, except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least (>)1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

General: Infrequent were chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. Rare were fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: Frequent were warm/cold sensations.

Cardiovascular: Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare was angina pectoris.

Digestive: Frequent were diarrhea and vomiting. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: Infrequent was dehydration.

Musculoskeletal: Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: Frequent were hypesthesia, mental acuity decreased, euphoria and tremor. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. Rare were: dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: Frequent was dyspnea. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: Frequent was flushing. Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital system: Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

The adverse experience profile seen with MAXALT-MLT Orally Disintegrating Tablets was similar to that seen with MAXALT Tablets.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of MAXALT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

No overdoses of MAXALT were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5 and 10 mg of MAXALT Tablets or MAXALT-MLT were effective for the acute treatment of migraines in adults. There is evidence that the 10-mg dose may provide a greater effect than the 5-mg dose (see *Clinical Studies*). Individuals may vary in response to doses of MAXALT Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10-mg dose with the potential risk for increased adverse events.

Redosing: Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Patients receiving propranolol: In patients receiving propranolol, the 5-mg dose of MAXALT should be used, up to a maximum of 3 doses in any 24-hour period. (See CLINICAL PHARMACOLOGY, *Drug Interactions.*)

For MAXALT-MLT Orally Disintegrating Tablets, administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

HOW SUPPLIED

No. 3732 — MAXALT Tablets, 5 mg, are pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other. They are supplied as follows:

NDC 0006-0266-06, unit of use carrying case of 6 tablets.

No. 3733 — MAXALT Tablets, 10 mg, are pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other. They are supplied as follows:

NDC 0006-0267-06, unit of use carrying case of 6 tablets.

No. 3800 — MAXALT-MLT Orally Disintegrating Tablets, 5 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified triangle on one side, and measuring 10.0-11.5 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3800-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

No. 3801 — MAXALT-MLT Orally Disintegrating Tablets, 10 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side, and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3801-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

Storage

Store MAXALT Tablets at room temperature, 15-30°C (59-86°F). Dispense in a tight container, if product is subdivided.

Store MAXALT-MLT Orally Disintegrating Tablets at room temperature, 15-30°C (59-86°F). The patient should be instructed not to remove the blister from the outer aluminum pouch until the patient is ready to consume the orally disintegrating tablet inside.

MAXALT Tablets are manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

By:
MSD, Ltd. Cramlington
Northumberland, NE23 9JU, UK

MAXALT-MLT Orally Disintegrating Tablets are manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

By:
Scherer DDS, Ltd.
Swindon, Wiltshire, SN5 8RU, UK

Issued ~~October 1998~~
Printed in USA

1. Annotated Package Circular

This section contains the annotated package circular. The annotations contain the references to the data located within the supplement.

Labeling Table of Contents for Supplemental NDA 20-864		
Description	**Paper Review volume number**	**Archive copy location folder/file name**
Labeling history	--	labeling/history.pdf
Labeling text		
a. Proposed labeling text	--	labeling/propose.pdf
b. Currently used labeling text	--	labeling/current.pdf
c. Last approved labeling text	--	labeling/approved.pdf
Final printed package insert	n/a	n/a
Carton label	n/a	n/a
Container label	n/a	n/a

Labeling History

a.) Complete list of the labeling changes being proposed in the current submission and the explanation for the changes.

CLINICAL PHARMACOLOGY, *Pharmacokinetics, Special Populations*

[redacted]

Age: The subheading "*Age*" has been revised to "*Elderly.*"

CLINICAL PHARMACOLOGY, *Clinical Studies*

[redacted]

PRECAUTIONS, *Pediatric Use*
The following statement has been added based on CSR 054: The efficacy of MAXALT Tablets (5 mg) in patients aged 12 to 17 years was not established in a randomized placebo controlled trial of 291 adolescent migraineurs (see *Clinical Studies*). Adverse events observed [redacted] were similar in nature to those reported in clinical trials in adults.

b.) The FDA approval date of the last approved labeling.

29 June 1998 (Original NDA)
Circular #9122100

c.) A history of all changes implemented since the last approved labeling.

8 January 1999 (Changes Being Effected) S-001
Circular #9122102

PRECAUTIONS, *Pregnancy*
A statement has been added to inform healthcare professionals of the pregnancy registry. Minor editorial revisions have been made.

ADVERSE REACTIONS
Minor editorial revisions have been made.

HOW SUPPLIED
The 500 count bottle of tablets has been deleted.

9 September 1999 (Annual Report)
Circular #9122101

COMPANY SIGNATURE
The site of manufacturing from the MAXALT Tablet and MAXALT-MLT Orally Disintegrating Tablets was added.

d.) A list of the supplements pending approval that may affect the review of the labeling in the current submission.

- 8 January 1999 (CBE) (S-001)
  Circular #9122102
- 15 January 1999 (Draft for Approval) (awaiting assignment of supplement number)

APPEARS THIS WAY
ON ORIGINAL

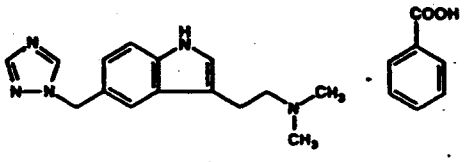
Currently Used Labeling Text
(#9122102)

MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT™
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

MAXALT* contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

MAXALT Tablets and MAXALT-MLT** Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. Rizatriptan has weak affinity for other 5-HT$_1$ receptor subtypes (5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$) and the 5-HT$_7$ receptor, but has no significant activity at 5-HT$_2$, 5-HT$_3$, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

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* Registered trademark of MERCK & CO., Inc.
** Trademark of MERCK & CO., Inc.

Pharmacokinetics.

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets, but the rate of absorption is somewhat slower with MAXALT-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-$HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-$HT_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

Age: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients, (creatinine clearance < 2 mL/min/1.73 m^2), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions (See also PRECAUTIONS, *Drug Interactions.*)

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when MAXALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and

41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions.*)

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS; DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of MAXALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Clinical Studies

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 1.

Table 1
Response Rates 2 Hours Following Treatment of Initial Headache

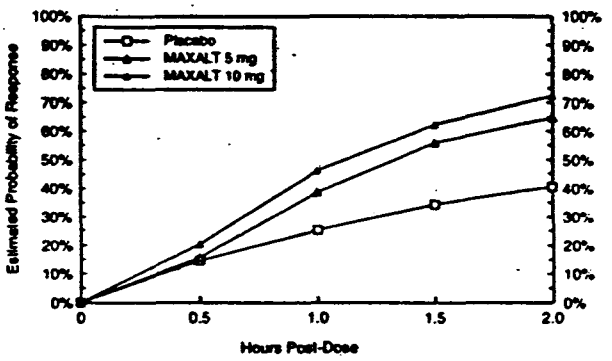
Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours††

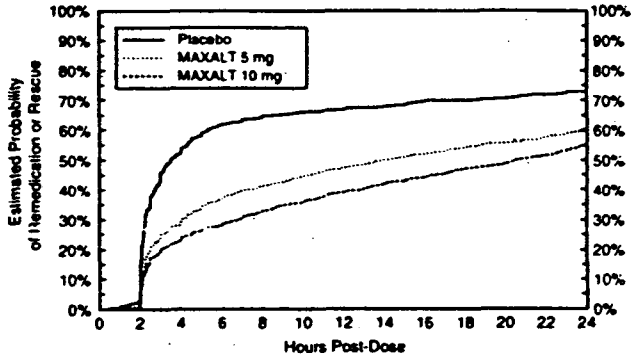


†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment†††



††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

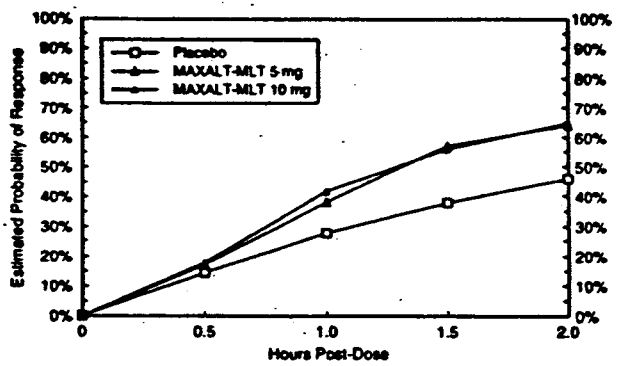
MAXALT-MLT Orally Disintegrating Tablets

The efficacy of MAXALT-MLT 5 mg and 10 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT-MLT were approximately 66% in either the MAXALT-MLT 5 mg and 10 mg groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT-MLT is depicted in Figure 3.

Figure 3: Estimated Probability of Achieving an Initial Headache Response with MAXALT-MLT by 2 Hours‡

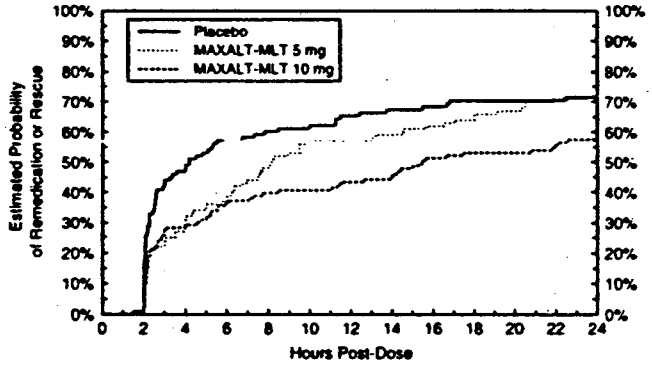


‡ Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 4.

Figure 4: Estimated Probability of Patients Taking a Second Dose of MAXALT-MLT or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment‡‡



‡‡ In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

INDICATIONS AND USAGE

MAXALT is indicated for the acute treatment of migraine attacks with or without aura in adults.

MAXALT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of MAXALT has not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

MAXALT should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm,

including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because MAXALT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

MAXALT should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

MAXALT is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

WARNINGS

MAXALT should only be used where a clear diagnosis of migraine has been established.

***Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:* Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, rizatriptan should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received rizatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of MAXALT and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use MAXALT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to rizatriptan.

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. Among the 3700 patients with migraine who participated in premarketing clinical trials of MAXALT, one patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Cerebrovascular Events and Fatalities Associated with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients

treated with other 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with MAXALT in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischemic ECG changes in clinical trials (one patient experienced chest pain with possible ischemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see CLINICAL PHARMACOLOGY, *Special Populations*).

Renally Impaired Patients: Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan (see CLINICAL PHARMACOLOGY, *Special Populations*).

Hepatically Impaired Patients: Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see CLINICAL PHARMACOLOGY, *Special Populations*).

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT-MLT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 5-mg orally disintegrating tablet contains 1.05 mg phenylalanine, and each 10-mg orally disintegrating tablet contains 2.10 mg phenylalanine.

Information for Patients

Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness has also been reported in some patients receiving MAXALT. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of MAXALT.

Physicians should instruct their patients to read the patient package insert before taking MAXALT. See the accompanying PATIENT INFORMATION leaflet.

MAXALT-MLT Orally Disintegrating Tablets

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT.

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions.*)

Propranolol: Rizatriptan 5 mg should be used in patients taking propranolol, as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70% (see CLINICAL PHARMACOLOGY, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Other 5-HT$_1$ agonists: The administration of rizatriptan with other 5-HT$_1$ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT$_1$ agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with rizatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. No clinical or pharmacokinetic interactions were observed when MAXALT 10 mg was administered with paroxetine.

Monoamine oxidase inhibitors: Rizatriptan should not be administered to patients taking MAO-A inhibitors and non-selective MAO inhibitors; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of rizatriptan and its metabolite (see CLINICAL PHARMACOLOGY, *Drug Interactions*; CONTRAINDICATIONS).

Drug/Laboratory Test Interactions

MAXALT is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The lifetime carcinogenic potential of rizatriptan was evaluated in a 100-week study in mice and a 106-week study in rats at oral gavage doses of up to 125 mg/kg/day. Exposure data were not obtained in those studies, but plasma AUC's of parent drug measured in other studies after 5 and 21 weeks of oral dosing in mice and rats, respectively, indicate that the exposures to parent drug at the highest dose level in the carcinogenicity studies would have been approximately 150 times (mice) and 240 times (rats) average AUC's measured in humans after three 10 mg doses, the maximum recommended total daily dose. There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis: Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, the *in vitro* mammalian cell mutagenesis assay in V-79 Chinese hamster lung cells, the *in vitro* alkaline elution assay in rat hepatocytes, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* chromosomal aberration assay in mouse bone marrow.

Impairment of Fertility: In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 225 times the exposure in humans receiving the maximum recommended

daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

Pregnancy: Pregnancy Category C

In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation with doses of 10 and 100 mg/kg/day. Maternal plasma drug exposures (AUC) at these doses were approximately 15 and 225 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The effects on offspring growth occurred in the absence of any apparent maternal toxicity in this study. The developmental no-effect dose was 2 mg/kg/day (maternal exposure approximately 1.5 times human exposure at the MRDD). The full spectrum of developmental toxicity is not known because adequately high doses, i.e., those producing some maternal toxicity, were not evaluated in the reproduction study. When higher, maternally toxic doses (250 mg/kg/day or greater) were evaluated over the same period of development in a rat dose range-finding study, pup mortality was increased.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses of 100 and 50 mg/kg/day, respectively, during organogenesis. Fetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses (maternal exposures approximately 225 and 115 times the human exposure at the MRDD in rats and rabbits, respectively). The developmental no-effect dose in these studies was 10 mg/kg/day in both rats and rabbits (maternal exposures approximately 15 times human exposure at the MRDD). Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to MAXALT while pregnant. Healthcare providers are encouraged to report any prenatal exposure to MAXALT by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

It is not known whether this drug 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. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatric Use

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, MAXALT is not recommended for use in patients under 18 years of age.

Use in the Elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with MAXALT is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n=17).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT Tablets. The most common adverse events during treatment with MAXALT were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension

studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Table 2 lists the adverse events regardless of drug relationship (incidence ≥ 2% and greater than placebo) after a single dose of MAXALT. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2
Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences
After a Single Dose of MAXALT Tablets or Placebo

	% of Patients		
Adverse Experiences	MAXALT 5 mg (N=977)	MAXALT 10 mg (N=1167)	Placebo (N=627)
Atypical Sensations	4	5	4
Paresthesia	3	4	<2
Pain and other Pressure Sensations	6	9	3
Chest Pain: tightness/pressure and/or heaviness	<2	3	1
Neck/throat/jaw: pain/tightness/pressure	<2	2	1
Regional Pain: tightness/pressure/heaviness	<1	2	0
Pain, location unspecified	3	3	<2
Digestive	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
Neurological	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4
Other			
Asthenia/fatigue	4	7	2

MAXALT was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of MAXALT: In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT (N=3716) and reported an event divided by the total number of patients exposed to MAXALT. All reported events are included, except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least (>)1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

General: Infrequent were chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. Rare were fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: Frequent were warm/cold sensations.

Cardiovascular: Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare was angina pectoris.

Digestive: Frequent were diarrhea and vomiting. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: Infrequent was dehydration.

Musculoskeletal: Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: Frequent were hypesthesia, mental acuity decreased, euphoria and tremor. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. Rare were: dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: Frequent was dyspnea. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: Frequent was flushing. Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital system: Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

The adverse experience profile seen with MAXALT-MLT Orally Disintegrating Tablets was similar to that seen with MAXALT Tablets.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of MAXALT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

No overdoses of MAXALT were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5 and 10 mg of MAXALT Tablets or MAXALT-MLT were effective for the acute treatment of migraines in adults. There is evidence that the 10-mg dose may provide a greater effect than the 5-mg dose (see *Clinical Studies*). Individuals may vary in response to doses of MAXALT Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10-mg dose with the potential risk for increased adverse events.

Redosing: Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Patients receiving propranolol: In patients receiving propranolol, the 5-mg dose of MAXALT should be used, up to a maximum of 3 doses in any 24-hour period. (See CLINICAL PHARMACOLOGY, *Drug Interactions.*)

For MAXALT-MLT Orally Disintegrating Tablets, administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

HOW SUPPLIED

No. 3732 — MAXALT Tablets, 5 mg, are pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other. They are supplied as follows:

NDC 0006-0266-06, unit of use carrying case of 6 tablets.

No. 3733 — MAXALT Tablets, 10 mg, are pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other. They are supplied as follows:

NDC 0006-0267-06, unit of use carrying case of 6 tablets.

No. 3800 — MAXALT-MLT Orally Disintegrating Tablets, 5 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified triangle on one side, and measuring 10.0-11.5 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3800-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

No. 3801 — MAXALT-MLT Orally Disintegrating Tablets, 10 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side, and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3801-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

Storage

Store MAXALT Tablets at room temperature, 15-30°C (59-86°F). Dispense in a tight container, if product is subdivided.

Store MAXALT-MLT Orally Disintegrating Tablets at room temperature, 15-30°C (59-86°F). The patient should be instructed not to remove the blister from the outer aluminum pouch until the patient is ready to consume the orally disintegrating tablet inside.

MAXALT Tablets are manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

By:
MSD, Ltd. Cramlington
Northumberland, NE23 9JU, UK

MAXALT-MLT Orally Disintegrating Tablets are manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA
By:
Scherer DDS, Ltd.
Swindon, Wiltshire, SN5 8RU, UK

Issued October 1998
Printed in USA

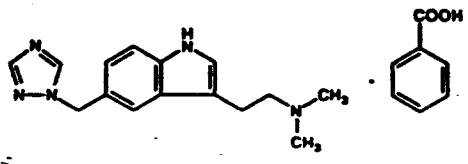
Last Approved Labeling Text
(#9122100)

MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT™
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

MAXALT* contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

MAXALT Tablets and MAXALT-MLT** Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. Rizatriptan has weak affinity for other 5-HT$_1$ receptor subtypes (5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$) and the 5-HT$_7$ receptor, but has no significant activity at 5-HT$_2$, 5-HT$_3$, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

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* Registered trademark of MERCK & CO., Inc.
** Trademark of MERCK & CO., Inc.

Pharmacokinetics

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets, but the rate of absorption is somewhat slower with MAXALT-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-$HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-$HT_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

Age: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients, (creatinine clearance < 2 mL/min/1.73 m^2), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions (See also PRECAUTIONS, *Drug Interactions.*)

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when MAXALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and

41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions*.)

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS; DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of MAXALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Clinical Studies

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 1.

Table 1
Response Rates 2 Hours Following Treatment of Initial Headache

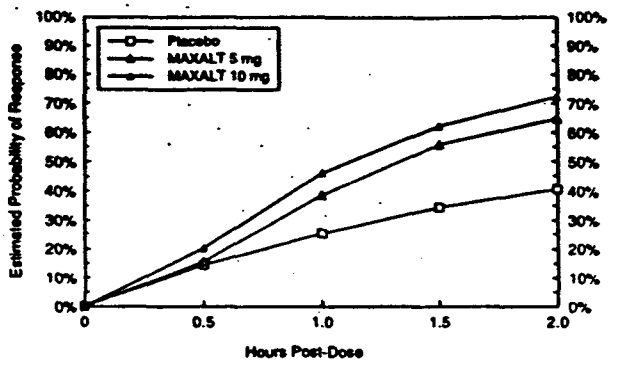
Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours††

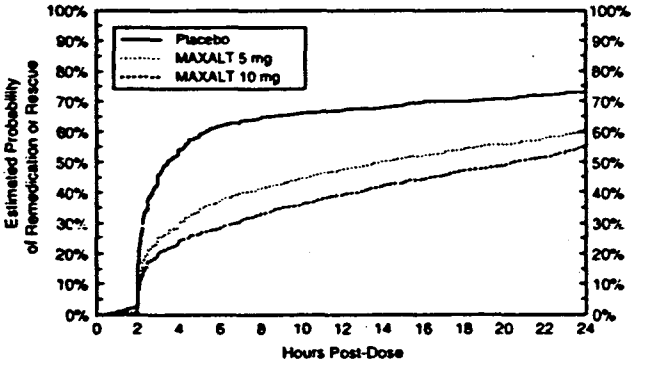


†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment†††



††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

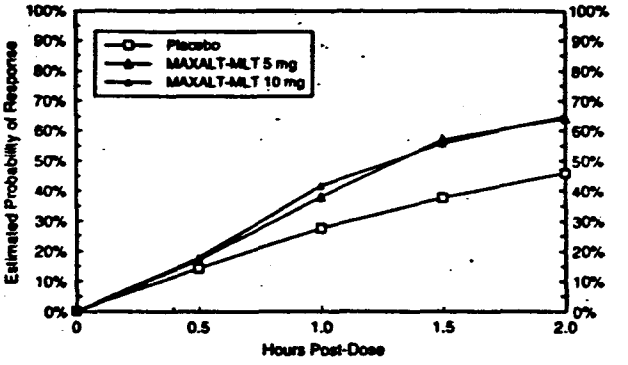
MAXALT-MLT Orally Disintegrating Tablets

The efficacy of MAXALT-MLT 5 mg and 10 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT-MLT were approximately 66% in either the MAXALT-MLT 5 mg and 10 mg groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT-MLT is depicted in Figure 3.

Figure 3: Estimated Probability of Achieving an Initial Headache Response with MAXALT-MLT by 2 Hours‡

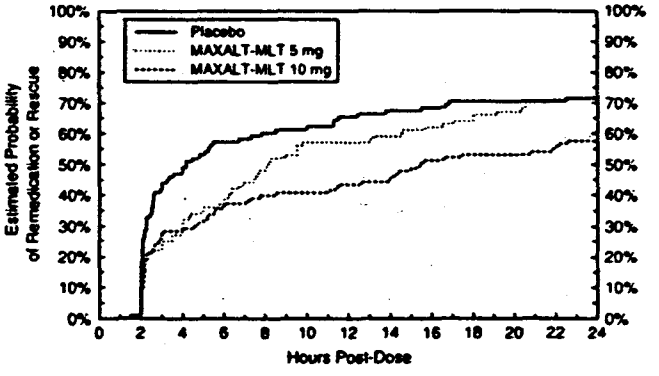


‡Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 4.

Figure 4: Estimated Probability of Patients Taking a Second Dose of MAXALT-MLT or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment‡‡



‡‡ In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

INDICATIONS AND USAGE

MAXALT is indicated for the acute treatment of migraine attacks with or without aura in adults.

MAXALT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of MAXALT has not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

MAXALT should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have

symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because MAXALT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

MAXALT should not be used within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

MAXALT is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

WARNINGS

MAXALT should only be used where a clear diagnosis of migraine has been established.

***Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:* Because of the potential of this class of compounds (5-HT$_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, rizatriptan should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received rizatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of MAXALT and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use MAXALT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to rizatriptan.

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT$_1$ agonists. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low. Among the 3700 patients with migraine who participated in premarketing clinical trials of MAXALT, one patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Cerebrovascular Events and Fatalities Associated with 5-HT$_1$ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT$_1$ agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT$_1$ agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT$_1$ agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT$_1$ agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

As with other 5-HT$_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with MAXALT in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischemic ECG changes in clinical trials (one patient experienced chest pain with possible ischemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT$_1$ agonist are candidates for further evaluation (see WARNINGS).

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see CLINICAL PHARMACOLOGY, *Special Populations*).

Renally Impaired Patients: Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan (see CLINICAL PHARMACOLOGY, *Special Populations*).

Hepatically Impaired Patients: Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see CLINICAL PHARMACOLOGY, *Special Populations*).

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT-MLT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 5-mg orally disintegrating tablet contains 1.05 mg phenylalanine, and each 10-mg orally disintegrating tablet contains 2.10 mg phenylalanine.

Information for Patients

Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness has also been reported in some patients receiving MAXALT. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of MAXALT.

Physicians should instruct their patients to read the patient package insert before taking MAXALT. See the accompanying PATIENT INFORMATION leaflet.

MAXALT-MLT Orally Disintegrating Tablets

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT.

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions.*)

Propranolol: Rizatriptan 5 mg should be used in patients taking propranolol, as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70% (see CLINICAL PHARMACOLOGY, *Drug Interactions*; DOSAGE and ADMINISTRATION).

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Other 5-HT$_1$ agonists: The administration of rizatriptan with other 5-HT$_1$ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT$_1$ agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with rizatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. No clinical or pharmacokinetic interactions were observed when MAXALT 10 mg was administered with paroxetine.

Monoamine oxidase inhibitors: Rizatriptan should not be administered to patients taking MAO-A inhibitors and non-selective MAO inhibitors; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of rizatriptan and its metabolite (see CLINICAL PHARMACOLOGY, *Drug Interactions*; CONTRAINDICATIONS).

Drug/Laboratory Test Interactions

MAXALT is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The lifetime carcinogenic potential of rizatriptan was evaluated in a 100-week study in mice and a 106-week study in rats at oral gavage doses of up to 125 mg/kg/day. Exposure data were not obtained in those studies, but plasma AUC's of parent drug measured in other studies after 5 and 21 weeks of oral dosing in mice and rats, respectively, indicate that the exposures to parent drug at the highest dose level in the carcinogenicity studies would have been approximately 150 times (mice) and 240 times (rats) average AUC's measured in humans after three 10 mg doses, the maximum recommended total daily dose. There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis: Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, the *in vitro* mammalian cell mutagenesis assay in V-79 Chinese hamster lung cells, the *in vitro* alkaline elution assay in rat hepatocytes, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* chromosomal aberration assay in mouse bone marrow.

Impairment of Fertility: In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 225 times the exposure in humans receiving the maximum recommended

daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

Pregnancy: Pregnancy Category C

In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation with doses of 10 and 100 mg/kg/day. Maternal plasma drug exposures (AUC) at these doses were approximately 15 and 225 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The effects on offspring growth occurred in the absence of any apparent maternal toxicity in this study. The developmental no-effect dose was 2 mg/kg/day (maternal exposure approximately 1.5 times human exposure at the MRDD). The full spectrum of developmental toxicity is not known because adequately high doses, i.e., those producing some maternal toxicity, were not evaluated in the reproduction study. When higher, maternally toxic doses (250 mg/kg/day or greater) were evaluated over the same period of development in a rat dose range-finding study, pup mortality was increased.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses of 100 and 50 mg/kg/day, respectively, during organogenesis. Fetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses (maternal exposures approximately 225 and 115 times the human exposure at the MRDD in rats and rabbits, respectively). The developmental no-effect dose in these studies was 10 mg/kg/day in both rats and rabbits (maternal exposures approximately 15 times human exposure at the MRDD). Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug 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. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatric Use

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, MAXALT is not recommended for use in patients under 18 years of age.

Use in the Elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with MAXALT is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n=17).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT Tablets. The most common adverse events during treatment with MAXALT were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Table 2 lists the adverse events regardless of drug relationship (incidence ≥ 2% and greater than placebo) after a single dose of MAXALT. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2
Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences
After a Single Dose of MAXALT Tablets or Placebo

	% of Patients		
Adverse Experiences	MAXALT 5 mg (N=977)	MAXALT 10 mg (N=1167)	Placebo (N=627)
Atypical Sensations	4	5	4
Paresthesia	3	4	<2
Pain and other Pressure Sensations	6	9	3
Chest Pain: tightness/pressure and/or heaviness	<2	3	1
Neck/throat/jaw: pain/tightness/pressure	<2	2	1
Regional Pain: tightness/pressure/heaviness	<1	2	0
Pain, location unspecified	3	3	<2
Digestive	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
Neurological	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4
Other			
Asthenia/fatigue	4	7	2

MAXALT was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of MAXALT: In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT (N=3716) and reported an event divided by the total number of patients exposed to MAXALT. All reported events are included, except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least (>)1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1,000 patients.

General: Infrequent were chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. Rare were fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: Frequent were warm/cold sensations.

Cardiovascular: Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare was angina pectoris.

Digestive: Frequent were diarrhea and vomiting. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: Infrequent was dehydration.

Musculoskeletal: Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: Frequent were hypesthesia, mental acuity decreased, euphoria and tremor. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. Rare were: dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: Frequent was dyspnea. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: Frequent was flushing. Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital system: Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

The adverse experience profile seen with MAXALT-MLT Orally Disintegrating Tablets was similar to that seen with MAXALT Tablets.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of MAXALT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

No overdoses of MAXALT were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5 and 10 mg of MAXALT Tablets or MAXALT-MLT were effective for the acute treatment of migraines in adults. There is evidence that the 10-mg dose may provide a greater effect than the 5-mg dose (see *Clinical Studies*). Individuals may vary in response to doses of MAXALT Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10-mg dose with the potential risk for increased adverse events.

Redosing: Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Patients receiving propranolol: In patients receiving propranolol, the 5-mg dose of MAXALT should be used, up to a maximum of 3 doses in any 24-hour period. (See CLINICAL PHARMACOLOGY, *Drug Interactions.*)

For MAXALT-MLT Orally Disintegrating Tablets, administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

HOW SUPPLIED

No. 3732 — MAXALT Tablets, 5 mg, are pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other. They are supplied as follows:

NDC 0006-0266-74, bottles of 500

NDC 0006-0266-06, unit of use carrying case of 6 tablets.

No. 3733 — MAXALT Tablets, 10 mg, are pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other. They are supplied as follows:

NDC 0006-0267-74, bottles of 500

NDC 0006-0267-06, unit of use carrying case of 6 tablets.

No. 3800 — MAXALT-MLT Orally Disintegrating Tablets, 5 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified triangle on one side, and measuring 10.0-11.5 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet).They are supplied as follows:

NDC 0006-3800-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

No. 3801 — MAXALT-MLT Orally Disintegrating Tablets, 10 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side, and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3801-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

Storage

Store MAXALT Tablets at room temperature, 15-30°C (59-86°F). Dispense in a tight container, if product is subdivided.

Store MAXALT-MLT Orally Disintegrating Tablets at room temperature, 15-30°C (59-86°F). The patient should be instructed not to remove the blister from the outer aluminum pouch until the patient is ready to consume the orally disintegrating tablet inside.

Dist. by
MERCK & CO., INC., West Point, PA 19486, USA

Issued June 1998
Printed in USA

Patent Submission Suggested Format

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information please refer to 21 C.F.R. 314.53.

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 20-864

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: MAXALT
- Active Ingredient(s): Rizatriptan Benzoate
- Strength(s): 5 mg and 10 mg
- Dosage Form: Tablet
- Approval Date: June 29, 1998

A. This section should be completed for each individual patent

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

U.S. Patent Number: 5,298,520

Expiration Date: January 28, 2012

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) X Y ___N
3. Method of Use X Y ___N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Treatment of acute migraine attacks.

Name of Patent Owner: MERCK, SHARP & DOHME, LTD., Licensed to MERCK & CO., INC.

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

U.S. Patent Number: 5,602,162

Expiration Date: February 11, 2014

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) ___Y X N
3. Method of Use ___Y X N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:_____

Name of Patent Owner: MERCK, SHARP & DOHME, LTD., Licensed to MERCK & CO., INC.

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

U.S. Patent Number:

Expiration Date:

Rockville, MD 20857

OR

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
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HFD-93 Room #235
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5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book.***

Previous Page

NDA 20-864: MAXALT 5 mg and 10 mg tablets
(RIZATRIPTAN BENZOATE)

Patent No.	*Patent Claim*	*Exp Date*	*Owned By*	*Licensee-Address*	*Licensee US Contact-Address*
5,298,520	drug substance; drug product; method of use	1/28/12	Merck Sharp & Dohme Ltd.	Merck & Co., Inc. One Merck Dr. Box 100 Whitehouse Station, NJ 08889-0100	Philippe L. Durette Merck & Co., Inc. 126 E. Lincoln Ave. RY 60-30 Rahway, NJ 07065-0900 732-594-4568
5,602,162	drug substance	2/11/14	Merck Sharp & Dohme Ltd.	Merck & Co., Inc. One Merck Dr. Box 100 Whitehouse Station, NJ 08889-0100	Philippe L. Durette Merck & Co., Inc. 126 E. Lincoln Ave. RY 60-30 Rahway, NJ 07065-0900 732-594-4568

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20864	**Trade Name:**	MAXALT(RIZATRIPTAN BENZOATE) 5MG/10MG TAB
Supplement Number:	2	**Generic Name:**	RIZATRIPTAN BENZOATE
Supplement Type:	SE5	**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP	**Proposed Indication:**	Sponsor proposes labeling changes based on studies in the adolescent population.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication, but is inadequate to support pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) _X_Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Required studies are ongoing

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Adolescent efficacy studies are negative. Labeling changes made appropriately.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LANA CHEN

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Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA SUPPLEMENT

Brand Name:	**Maxalt**
Generic Name:	**rizatriptan**
Sponsor:	**Merck**
Indication:	**migraine**
NDA Number:	**20-864 SE5-02**
Original Receipt Date:	**10/27/99**
Clinical Reviewers:	**Armando Oliva, MD**
Review Author:	**Armando Oliva, MD**
Review Completed:	**2/24/00**

Table of Contents

1. Background

Maxalt (rizatriptan) is approved in adults for the acute treatment of migraine. It is available as a tablet or orally-disintegrating tablet (MLT) in 5mg and 10mg strengths. This efficacy supplement contains the results of 2 clinical trials in adolescent migraineurs (12-17 years of age) and provides for changes in the label to include the results of these adolescent studies.

The first study is a clinical pharmacology study which compares the PK of rizatriptan and its minor n-monodesmethyl metabolite in 12 healthy adolescent migraineurs between attacks (study 048) using adult historical control PK data. The second study is a short-term, single attack efficacy and safety study also in adolescent migraineurs (study 054). This study, the sponsor reports, failed to demonstrate efficacy of rizatriptan in the adolescent population.

The sponsor has also submitted the same proposed labeling changes to NDA 20-865, which is the Maxalt MLT formulation, since both formulations share the same label.

The sNDA was submitted entirely in electronic format suitable for archive in accordance with the electronic NDA guidance document, and it is this electronic sNDA which I used for my review.

2. Proposed Changes to Labeling

I describe the sponsor's proposed labeling changes below.

Clinical Pharmacology: Special Populations
The following new section appears:

The title of the "Age" section is now changed to "Elderly" since this section (which is otherwise unchanged) describes the PK in the elderly.

Clinical Pharmacology: Clinical Studies

Between the sections that describe efficacy of the tablet and MLT formulations in adults, a new paragraph appears:

In a single study in adolescents (n=291),

Precautions: Pediatric Use
The following new paragraph appears after the first paragraph (which already does not recommend Maxalt in patients under 18 years of age).

The efficacy of Maxalt (5 mg) in patients aged 12 to 17 was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see Clinical Studies). Adverse events observed were similar in nature to those reported in clinical trials in adults.

3. Commercial Marketing History

The sponsor reports that as of 10/15/99, Maxalt has received marketing approval in 47 countries, including the US, UK, Canada, Western Europe, and Australia. No marketing application has been rejected in any country, nor has approval been suspended, revoked, or withdrawn in any country. There is no mention whether rizatriptan is approved for pediatric use in any country.

4. Study 048 – Adolescent PK Study

I do not review the adolescent PK study in any great detail. I refer the reader to the biopharm review for a more detailed review.

This was an open-label single dose study to investigate the pharmacokinetics and safety of rizatriptan in adolescent migraineurs (12-18 years). A single Maxalt 10mg tablet was given to each subject outside of a migraine attack. A total of 12 subjects participated in the study (6 males and 6 females). The actual age range studied was 13-18 years. All 12 completed this single dose study.

The objective was to compare the plasma concentration profiles of rizatriptan and the n-desmethyl metabolite in this population with historical adult controls, and to assess the safety and tolerability in this age group.

The study recruited nonsmoking subjects with a history of migraine who were otherwise healthy.

Adult control data were obtained from studies 15, 16, 19, 35, 36, 37, 42, and 43 (submitted in the original NDA). The sponsor compared the adolescent data generated from this study with data from study 35, and also with pooled adult data from all of these studies. The $AUC_{0\rightarrow\infty}$ comparisons are shown in Table 1 (sponsor summary table, p048.pdf, page 11).

The geometric means estimates for adolescents depends on the historical control group that was used, hence the different values for each comparison. AUC's were generally higher in adolescents, compared to historical adult controls. This difference was not seen in males, but was evident in females.

Table 1: $AUC_{0\rightarrow\infty}$ (Geometric Means) for Rizatriptan 10mg Single Oral Dose

Gender	Geometric Mean $AUC_{0\rightarrow\infty}$ (ng.hr/mL)			Geometric Mean Ratio (Adol/Adults) and 90% CI	
	Adolescents Protocol 048	Adults Protocol 035	Adults Pooled	Adults Protocol 035	Adults Pooled
Females	108.72	70.32	--	1.55 (1.27, 1.89)	--
	103.66	--	76.81	--	1.35 (0.97, 1.87)
Males	66.88	65.34	--	1.02 (0.81, 1.29)	--
	66.80	--	73.36	--	0.91 (0.67, 1.23)
Pooled	85.27	67.78	--	1.26 (1.09, 1.46)	--
	82.68	--	73.83	--	1.12 (0.84, 1.50)

The C_{max} results are shown in Table 2 (sponsor summary table, p048.pdf, page 11). As was seen with AUC, C_{max} was generally higher in adolescents, although this effect seemed to come exclusively from the female subgroup.

Table 2: C_{max} (Geometric Means) for Rizatriptan 10mg Single Oral Dose

Gender	Geometric Mean C_{max} (ng/mL)			Geometric Mean Ratio (Adol/Adults) and 90% CI	
	Adolescents Protocol 048	Adults Protocol 035	Adults Pooled	Adults Protocol 035	Adults Pooled
Females	30.96	20.22	--	1.53 (1.07, 2.19)	--
	35.39	--	23.48	--	1.51 (1.00, 2.28)
Males	21.80	20.12	--	1.08 (0.75, 1.56)	--
	21.37	--	23.06	--	0.93 (0.59, 1.47)
Pooled	25.98	20.17	--	1.29 (1.01, 1.64)	--
	27.21	--	22.77	--	1.19 (0.81, 1.76)

Similar findings in AUC and C_{max} were noted with the n-desmethyl metabolite.

T_{max} was similar to adults at about 1 hour. $T_{1/2}$ was numerically slightly shorter in adolescents compared to adults (1.6 – 1.8 hours, compared to 1.8 – 2 hours in adults).

All subjects underwent laboratory evaluations (hematology, chemistry, urinalysis), vital signs, ECG's and physical examinations during the study.

There were no deaths and no serious adverse events. Three of the 12 patients reported adverse events, two of which were rated as possibly drug related.

One subject (0008) experienced hypotension after dosing. Baseline BP was 110/73, and 0.5, 1, 2, and 3 hour BP's were 116/74, 114/72, 98/58, ad 116/74. Therefore, the 2 hour BP was low, which resolved at 3 hours. The duration was approximately 1.5 hours and this was considered possibly drug related. It's not reported whether there were any symptoms associated with this finding (*i.e.*, lightheadedness, dizziness, etc.). A separate line listing shows that this subject did report dizziness at 30 minutes post-dose, but since the hypotension occurred later, it's not clear if the two events were related. This subject also reported nausea at 30 minutes.

A second subject (0004) reported a migraine at on the third day post-dosing. This was not considered drug-related. A third subject (0011) reported a severe headache post-dose. This was rated possibly drug-related.

Laboratory tests, ECG's and physical exams revealed no clinically significant deviations from baseline.

Overall, the study did not reveal any clinically significant safety concerns.

5. Study 054 – Adolescent Efficacy Study

5.1 Protocol Description

The title of this study was "A randomized, double blind, placebo-controlled, parallel group, outpatient study to examine the safety, tolerability, and efficacy of rizatriptan 5mg p.o. for the acute treatment of migraine in adolescents.

This was a multicenter study which was conducted in 19 centers in the United States. The study began in 11/97 and was completed in 7/98. The duration of treatment was a single day.

The objectives were to examine the efficacy, safety, and tolerability of Maxalt 5mg tablets in adolescents (12-17 years of age).

Patients were otherwise healthy male or female between 12-17 years of age, with a history of migraine with or without aura, according to IHS criteria, for the six months prior to the start of the study. Patients with predominantly mild attacks, and those with hemiplegic or basilar migraine were excluded. Also excluded were pregnant or nursing females.

Eligible patients were randomized to Maxalt 5mg tablets or placebo, stratified by age (12-14 and 15-17). Patients were instructed to take a single dose of study medication at the onset of a moderate or severe migraine. Two additional doses, the same as the initial dose (*i.e.*, non-randomized) were permitted within 24 hours to treat headache recurrence. Rescue was permitted after 2 hours for persistent pain.

Efficacy measures were recorded in a patient diary at 0, 0.5, 1, 1.5, 2, 3, and 4 hours. Safety measures included pre- and post-treatment vital signs, laboratory, and ECG data, as well as incidence of adverse events.

Headache severity was rated on a four point scale (0=none, 1=mild, 2=modeate, 3=severe). A response at 2 hours was defined in the usual manner, *i.e.*, a grade 2/3 headache at baseline and grade 0/1 headache at 2 hours.

The primary efficacy analysis compared the proportion of patients achieving pain-free at 2 hours (the 2-hr complete relief rate) between drug and placebo, and was based on the ITT population, which was designated in the protocol as the "all patients treated" analysis – *i.e.*, it included all patients who received study medication and had at least one record

of pain severity within 2 hours after the initial dose (n=291). The analysis used a logistic regression model.

This primary endpoint was chosen based on new IHS guidelines which recommend the use of pain-free as primary endpoint in future clinical trials with investigational migraine compounds, as well as experience in the adult trials which suggested it may be a more suitable endpoint for study. Finally, it may be an easier endpoint for adolescents to understand and use accurately.

Secondary endpoints included the "classic" 2-hr headache response rate, proportion of patients with nausea, vomiting, photophobia, phonophobia, no functional disability at 2 hours, the proportion requiring a second dose or rescue within 24 hours, and the proportion achieving a response to a second dose for headache recurrence. Also analyzed were pain-free and pain-response rates at other endpoints, time to pain-free and time to pain-response.

The study had 95% power to detect a 20 percentage point difference between the rizatriptan and placebo groups with planned sample sizes of 120 evaluable patients in each of the treatment groups based on a two-tailed test with α=0.05.

All 296 patients who took study medication were included in the safety analysis, which compared the incidences of AE's reported by patients prior to taking a second dose of study medication. Treatment comparisons used Fisher's exact test.

5.2 Patient Accounting

A total of 360 patients entered the study (Table 3, sponsor table 11, study report p054.pdf, page 51) and a total of 289 completed the study. The majority of those who discontinued (64 of 71) did so because they did not take study drug. Two-hundred ninety-six (296) actually took study medication.

Table 3: Patient Accounting

	Riza 5 mg	PBO	Total
Patients Entered	**179**	**181**	**360**
Male (age range)	48 (12-14)	50 (12-14)	90 (12-14)
	31 (15-17)	36 (15-17)	67 (15-17)
Female (age range)	48 (12-14)	48 (12-14)	96 (12-14)
	52 (15-17)	46 (15-17)	98 (15-17)
Completed	148	141	289
Discontinued: Total	31	40	71
Clinical AE	0	0	0
Laboratory AE	0	0	0
Did not take study drug	30	34	64
Other	1	6	7
Patients Treated	**149**	**147**	**296**
Completed	148	141	289
Discontinued due to:			
Clinical AE	0	0	0
Lost to follow-up	0	4	4
Incl/excl criteria not met	1	0	1

	Riza 5 mg	PBO	Total
Patient uncooperative	0	2	2
Patients Not Treated	**30**	**34**	**64**
Discontinued due to:			
Lack of migraine attack	13	18	31
Lost to follow-up	4	4	8
Patient uncooperative	1	2	3
Withdrew from study	1	2	3
Abnormal pre-study labs	2	0	2
Abnormal baseline ECG	5	6	11
Study terminated	2	1	3
Incl/excl criteria not met	2	0	2
Incapable of completing diary	0	1	1

All the results presented in this section pertain to the 296 patients who took study medication. Baseline patient characteristics are shown in Table 4 (sponsor table 6, study report p054.pdf, page 44).

Table 4: Baseline Patient Characteristics

	Riza 5mg (n=149)		PBO (n=147)		Total (n=296)	
	n	%	n	%	n	%
Gender						
Male	66	(44.0)	69	(47.0)	135	(46.0)
Female	83	(56.0)	78	(53.0)	161	(54.0)
Age (Years)						
12 to 14	81	(54.0)	75	(51.0)	156	(53.0)
15 to 17	68	(46.0)	71	(48.0)	139	(47.0)
>17	0	(0.0)	1	(1.0)	1	(0.3)
Mean	14.3		14.4		14.4	
SD	1.6		1.8		1.7	
Median	14.0		14.0		14.0	
Range	12-17		12-18		12-18	
Racial Origin						
Caucasian	137	(92.0)	136	(93.0)	273	(92.0)
Black	5	(3.0)	8	(5.0)	13	(4.0)
Hispanic	6	(4.0)	3	(2.0)	9	(3.0)
Hispanic/White	1	(1.0)	0	(0.0)	1	(0.3)
Baseline Severity						
Missing	0	(0.0)	5	(3.0)	5	(2.0)
Moderate	94	(63.0)	78	(53.0)	172	(58.0)
Severe	55	(37.0)	64	(44.0)	119	(40.0)
Presence of Aura						
Without	135	(91.0)	137	(93.0)	272	(92.0)
With	14	(9.0)	10	(7.0)	24	(8.0)
Prophylactic Treatment						
Without	133	(89.0)	142	(97.0)	275	(93.0)
With	16	(11.0)	5	(3.0)	21	(7.0)
β-blockers	1	(1.0)	1	(1.0)	2	(1.0)
Calcium channel blockers	1	(1.0)	0	(0.0)	1	(0.0)
SSRI	13	(9.0)	4	(3.0)	17	(6.0)
Tricyclic antidepressants	4	(3.0)	0	(0.0)	4	(1.0)
Valproate	1	(1.0)	0	(0.0)	1	(0.0)

	Riza 5mg (n=149)		PBO (n=147)		Total (n=296)	
	n	%	n	%	n	%
Oral Contraceptive / Women						
Without	81	(98.0)	70	(90.0)	151	(94.0)
With	2	(2.0)	8	(10.0)	10	(6.0)

The patients' ages ranged from 12-18 years (one was 18 years old; all others were 17 and younger). The mean age was 14.4 years. For simplicity, the one 18 year old was included in all the 15-17 year-old age group in all analyses and summary tables.

Slightly over half (54%) of the population was female[1], and the majority (92%) were Caucasian. The treatment groups were similar with regard to age, gender, and race.

About 58% had a moderate headache at baseline, and 40% treated a severe headache. The remaining 2% (n=5) had a missing headache severity score at baseline. More patients had a moderate headache at baseline in the rizatriptan group compared to the placebo group (63% vs. 53%); however, this difference was not nominally significant (p=0.176).

Twenty-four patients reported an aura (8%). About 7% were using migraine prophylaxis concomitantly. About 6% of the female population were using oral contraceptives (n=10).

Of the 296 patients who took study medication, 5 patients (all in the placebo group) recorded neither the baseline evaluation nor any post-treatment evaluations. These 5 were excluded from all efficacy analyses. Therefore, a total of 291 patients were in the ITT or "all patients treated" population. All 296 patients were included in the safety population.

5.3 Efficacy

The primary efficacy endpoint was the percentage of patients who were pain-free at 2 hours. This is shown in Table 5 (sponsor table 15, study report p054.pdf, page 56). The 2-hour pain-free rate was numerically higher in the rizatriptan group compared to placebo (32.2% vs. 28.2%) but the 95% confidence intervals overlapped considerably, resulting in lack of statistical significance (p=0.474). This numeric advantage was seen at 1.5 hours after dosing and all time points thereafter, but the differences were not statistically significant.

Table 5: Proportion of Patients Pain-Free at Two Hours (All Patients Treated)

Treatment	N	n	%	95% CI
Rizatriptan 5 mg	149	48	32.2	24.8 to 40.4
PBO	142	40	28.2	20.9 to 36.3

[1] Reviewer's note: the sex distribution differs from the typical adult migraine trial population, which tends to be overwhelmingly female.

Secondary endpoints included the percentage who had a pain response at 2 hours, were without functional disability at 2 hours, had associated symptoms at 2 hours, used additional analgesic/antiemetic medication or a second dose of test medication after the initial dose, and had a response after treatment for recurrence. These results are shown in Table 6 (study report p054.pdf, page 14). Although the results numerically favored rizatriptan in general, only the analysis of the proportion who had no functional disability at 2 hours reached nominal significance. It is noted that the placebo response rate in this study was very high at 55.6%, which is similar to the high placebo response rates seen in other adolescent acute migraine studies which this reviewer has seen.

Table 6: Secondary Endpoints

	Rizatriptan 5mg		PBO	
	N	%	N	%
% response at 2 hours	149	65.8	142	55.6
% with no functional disability at 2 hours	149	44.3*	142	35.9
% with associated symptoms at 2 hours:				
Photophobia	149	39.6	142	43.7
Phonophobia	149	29.5	142	31.0
Nausea	149	18.8	142	27.5
Vomiting	149	2.7	142	2.1
% Using additional analgesic/antiemetics or a second dose of test medication within 24 hours after the initial dose	149	39.0	142	46.0

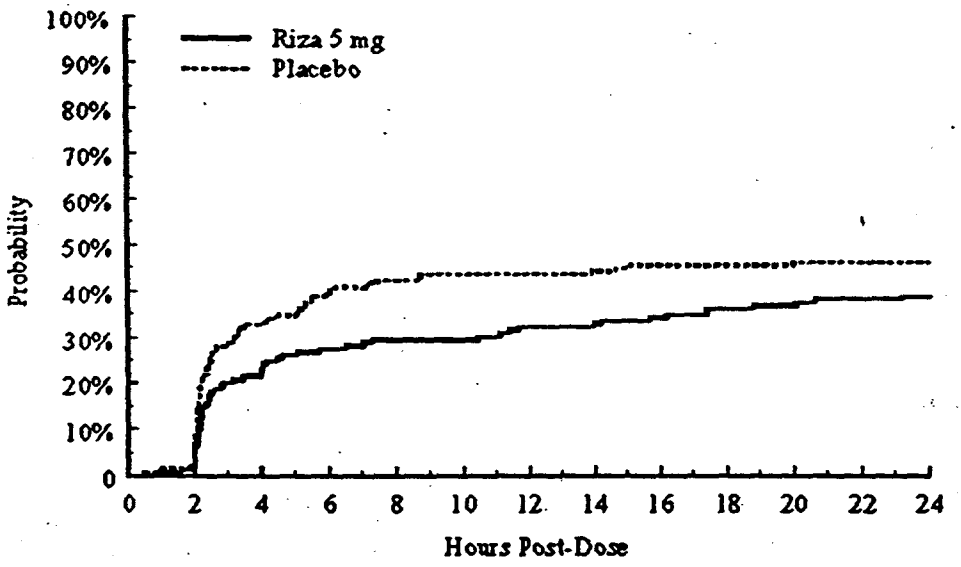
*p<0.05

Migraine recurrence was defined as the return of headache to grade 2 or 3 within 24 hours of the initial dose in patients who reported a pain response (grade 0 or 1) at 2 hours. Of the 177 patients who responded at 2 hours post dose, a total of 25 (14%) had a migraine recurrence within 24 hours. The percentages having recurrence were 11% and 18% in the rizatriptan 5mg and placebo groups, respectively. No formal statistical test was performed.

The 2-hr response rates for a second dose of study medication taken to treat recurrence were approximately 73% and 69% for the rizatriptan and placebo groups, respectively. Again, no statistical test was performed.

The probability of taking a 2nd dose or rescue during the first 24 hours is shown in Figure 1 (sponsor figure 6, study report p054.pdf, page 87). Over the 24-hour post dose period, the percentage of rizatriptan patients who remedicated was 39%, compared to 46% for placebo. This was not nominally significant (p=0.125).

Figure 1: Probability of Taking a 2nd Dose or Rescue within 24 Hours Post Dose



5.4 Safety

All 296 patients who took study medication were included in the safety database.

There were no deaths.

There was one serious adverse event reported. This was a 15 year-old female who took one dose of placebo on day 1. On day 2, she returned for follow-up visit and had a normal physical examination, laboratory tests, and ECG. On day 15, she presented with severe headache, dizziness, vertigo, and vomiting of 48 hours duration, and loss of consciousness twice. MRI, CT, LP were normal. A diagnosis of prolonged vertebrobasilar migraine was made. This was not felt to be related to study medication by the investigator.

There were no adverse dropouts, which is not unusual in a single attack study of this design since the opportunity to drop out was small.

About one-third (33.6%, 50/149) of the rizatriptan-treated patients reported at least one AE during the study, compared to only a slightly higher incidence (35.4%, 52/147) for the placebo group. The most common adverse events reported were: dry mouth, dizziness, asthenia/fatigue, nausea, and somnolence. These are similar to those seen in the adult population.

The sponsor used two methods to analyze adverse events. The first method calculated the incidence of all adverse events reported between the first dose and the post-treatment visit (regardless of number of doses taken). The second method calculated the incidences of all AE's reported prior to taking a 2nd dose. Most patients who reported an adverse event did so prior to taking a 2nd dose (50/50, 100% for rizatriptan group, and 52/53, 98% for the placebo group); therefore, the first method appears to be a reasonable method to

identify important treatment-associated events in this study. The incidences of the most commonly reported AE's prior to taking a 2nd dose are shown in Table 7 (sponsor table 45, study report p054.pdf, page 103-104).

Table 7: Adverse Event Summary Table (Prior to 2nd Dose; ≥1% Incidence)

	Rizatriptan 5mg (n=149)			PBO (n=147)		
	n	(%)	DR	n	(%)	DR
Patients with ≥1 AE	**50**	**(33.6)**	**33**	**52**	**(35.4)**	**35**
Patients with no AE	**99**	**(66.4)**		**95**	**(64.6)**	
Body as a Whole/Site Unspecified	**11**	**(7.4)**	**8**	**6**	**(4.1)**	**3**
Asthenia/fatigue	5	(3.4)	5	3	(2.0)	3
Cold sensation	2	(1.3)	2	0		
Pain, abdominal	4	(2.7)	2	2	(1.4)	1
Pain, chest	1	(0.7)		2	(1.4)	1
Cardiovascular System	**2**	**(1.3)**	**1**	**1**	**(0.7)**	**1**
Cold extremities	2	(1.3)	1	0		
Digestive System	**15**	**(10.1)**	**11**	**19**	**(12.9)**	**12**
Diarrhea	2	(1.3)	2	2	(1.4)	
Dry mouth	7	(4.7)	6	5	(3.4)	5
Dyspepsia	2	(1.3)		0		
Nausea	4	(2.7)*	3	12	(8.2)	6
Musculoskeletal System	**8**	**(5.4)**	**4**	**4**	**(2.7)**	**2**
Pain, neck	3	(2.0)	2	2	(1.4)	2
Nervous System & Psychiatric	**19**	**(12.8)**	**15**	**23**	**(15.6)**	**17**
Dizziness	7	(4.7)	5	7	(4.8)	6
Euphoria	2	(1.3)	2	0		
Headache	4	(2.7)	3	1	(0.7)	1
Hypesthesia	4	(2.7)	3	0		
Paresthesia	2	(1.3)	2	0		
Somnolence	4	(2.7)*	3	12	(8.2)	9
Tremor	0			2	(1.4)	1
Respiratory System	**7**	**(4.7)**	**4**	**12**	**(8.2)**	**1**
Congestion, nasal	1	(0.7)		3	(2.0)	
Infection, respiratory, upper	1	(0.7)		3	(2.0)	
Pharyngitis	1	(0.7)		3	(2.0)	
Skin & Skin Appendage	2	(1.3)	1	2	(1.4)	
Special Senses	**7**	**(4.7)**	**6**	**5**	**(3.4)**	**1**
Blurred vision	0			2	(1.4)	
Pain, eye	2	(1.3)	1	0		
Perversion, taste	2	(1.3)	1	1	(0.7)	1
Urogenital System	**2**	**(1.3)**		**2**	**(1.4)**	**2**
Hot flashes	0			2	(1.4)	2

DR = "drug-related"
*p<0.05 compared to placebo

The following table shows the incidence of AE's reported prior to the second dose, according to age (Table 8, sponsor table 50, study report p054.pdf, page 117). In general, the incidence of the more common AE's (with the exception of headache) was higher in

the older age group. However, due to the small numbers of events reported, the clinical relevance of this finding is unclear.[2]

Table 8: Adverse Event Summary Table, by Age (Prior to 2nd Dose, ≥3% Incidence)

	12-14						15-17					
	Rizatriptan 5mg (n=81)			PBO (n=75)			Rizatriptan 5mg (n=68)			PBO (n=72)		
Adverse Event	N	%	DR	n	%	DR	n	%	DR	n	%	DR
Asthenia/fatigue	1	1.2	1	2	2.7	2	4	5.9	4	1	1.4	1
Pain, abdominal	1	1.2	1	0	0	0	3	4.4	1	2	2.8	1
Dry mouth	1	1.2	1	2	2.7	2	6	8.8	5	3	4.2	3
Nausea	1	1.2	0	3	4.0	2	3	4.4	3	9	12.5	4
Dizziness	1	1.2	1	4	5.3	3	6	8.8	4	3	4.2	3
Headache	3	3.7	2	1	1.3	1	1	1.5	1	0	0	0
Somnolence	1	1.2	1	6	8.0	4	3	4.4	2	6	8.3	5
Respiratory, upper	1	1.2	0	3	4.0	0	0	0	0	0	0	0

Since this was an outpatient study, follow-up vital signs, ECG's, and laboratory tests were done days after treatment. This lowers the sensitivity significantly of these tests.

Five patients, 2 in rizatriptan group and 3 in placebo group, had clinically significant vital sign abnormalities at follow-up. There were no clinical correlates with any of the findings. All were associated with drop in systolic blood pressure, diastolic blood pressure, or pulse. No clinically significant elevations in blood pressures were seen.

There were no serious ECG AE's and no ECG AE dropouts. One patient, a 14 year-old female in the placebo group, had an ECG AE (abnormal P axis and abnormal atrial rhythm) on post-treatment day 7 that was not serious and considered not drug related by the investigator. The pre-treatment ECG tracing was normal and the finding was not associated with a clinical AE. No follow-up information was available.

There were no serious laboratory AE's, and no laboratory AE dropouts. Six patients, 3 in each of the treatment groups, had laboratory AE's at the post-treatment visit. One patients in the rizatriptan group was considered to have a possible drug-related laboratory AE. There were no clinical correlates to the laboratory AE's reported.

In the placebo group, a 17 year old male had an elevated ALT of 52 (ULN 43 U/L) 9 days after placebo treatment. The test was normal 25 days later. A 16 year old male had a creatinine of 1.5 mg/dL at the post-treatment visit, which occurred 23 days after treatment with placebo. All other labs were unremarkable. No follow-up was given. A 15 year-old maled had an ALT of 02 U/L and AST of 131 U/L (ULN 36 U/L) and WBC was 4.03K/mm^3 (LLN 4.43K/^{mm3}) on day 14 after treatment with placebo. Repeat tests were normal 6 days later.

[2] In contrast, the sumatriptan tablet labeling describes a larger adolescent safety database which reports a higher incidence of AE's in the younger age group. These data do not support such a finding with rizatriptan. Since this database is small, I suggest we remain silent in labeling regarding any age-related differences in adverse events.

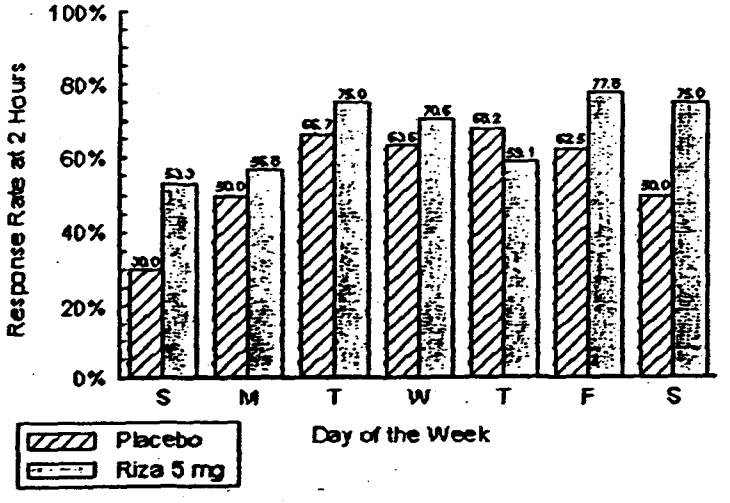
in the rizatriptan group, the only one felt to be possibly related to treatment was as 12 year-old male who had a total bilirubin of 1.5 mg/dL (ULN 1.2 mg/dL) and an elevated glucose of 199 mg/dL at post-treatment day 7. Both tests were normal 7 days later. The other two abnormalities were in a 12 year-old male with 2+ proteinuria at post-treatment day 48, which was unchanged 13 days later, and in a 13 year-old male that had trace proteinuria at post-treatment day 11. Repeat testing 7 days later was normal.

There were 7 patients who had clinically significant laboratory abnormalities. Four (4) occurred in the placebo group, and 3 occurred in the rizatriptan group. Only 1 was associated an adverse event (elevated ALT on placebo). Four events (1 on rizatriptan, 3 on placebo) were decreased hemoglobin and/or hematocrit. One was an elevated eosinophil percentage at baseline in a rizatriptan-treated patient. The last one was an elevated bilirubin of 2.5 mg/dL noted 48 days after treating a migraine attack with rizatriptan 5mg.

5.5 Post-Hoc Sponsor Analyses

In an attempt to understand the high placebo response rate seen in this study, the sponsor performed additional analyses of efficacy by weekday (Figure 2, sponsor figure 7, study report p054.pdf, page 95). These demonstrated that patients who were treated with rizatriptan on weekends (*i.e.*, non-school days) had statistically superior response compared to those patients who were treated on weekdays. Placebo response rates on weekends were generally lower than during weekdays. The sponsor suggests that during a weekday, when patients were likely to be in school, treatment may have been delayed until after school. With this hypothesized delay, the headaches in these patients may have been spontaneously resolving, resulting in a high placebo response rate. The sponsor plans to test this hypothesis in a future study.

Figure 2: Two-Hour Headache Response Rates by Day of the Week



5.6 Sponsor's Conclusions

The sponsor concluded from this study that rizatriptan 5mg

- is not statistically superior to placebo in adolescents as measured by the 2-hour complete pain relief and headache response rates.
- is superior to placebo in reducing functional disability at 1.5 and 2 hours post dose.
- is well tolerated for the acute treatment of migraine in adolescent patients.

5.7 Reviewer's Analyses

Since the sponsor-provided primary efficacy analysis is negative and their conclusion is that rizatriptan has not been shown to be effective in this population, I saw no need to repeat any of their analyses.

5.8 Reviewer's Conclusions

I conclude from this study that rizatriptan 5mg

- has not been shown to be effective for the acute treatment of migraine in adolescents.
- is not associated with a significant safety concerns in this population.

I do not accept the sponsor's conclusion regarding effect on functional disability. To my knowledge, the functional disability measure is not a validated measure of clinical migraine disability (and the sponsor has not provided any information otherwise). Furthermore, the functional disability analysis in this study was a secondary analysis and the result carries no statistical inferential ability. Therefore, no conclusions regarding the effects of rizatriptan 5mg on functional migraine disability can be made from this study.

6. Labeling Review

The sponsor proposes minor changes to labeling as described in section 2, page 3 of this review, which I repeat with comments below.

Clinical Pharmacology: Special Populations
Sponsor proposed:

The "Age" section is now titled "Elderly" since it describes the PK in the elderly.

I defer comment on this section to the biopharm review.

Clinical Pharmacology: Clinical Studies

Between the sections that describe efficacy of the tablet and MLT formulations in adults, the sponsor proposes:

In a single study in adolescents (n=291),

I have several comments regarding this statement:

1. The sumatriptan tablet labeling, which also contains information about negative pediatric (adolescent) studies, does not describe these studies in the clinical pharmacology section. The Precautions:Pediatric use section contains all the information about these studies.

[redacted]

Table 9: (Labeling Table 1) – Response Rates 2 Hours Following Treatment of Initial Headache

[redacted]

2. If we keep the sentence, the term "relief" should be changed to "response" to maintain consistency with the rest of the clinical studies section.

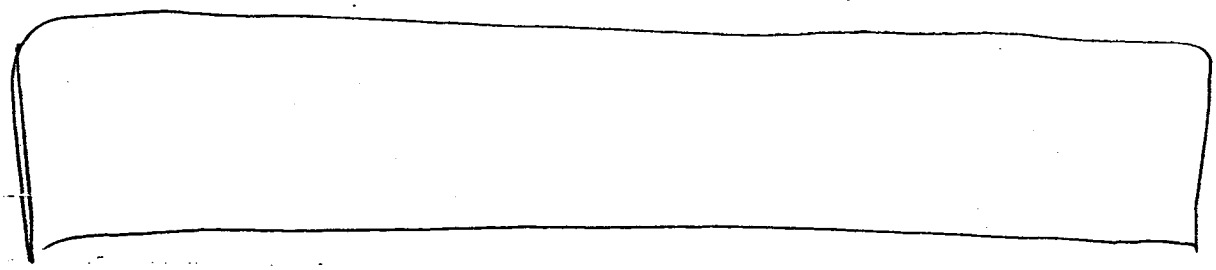
3. The sentence reports the results of a secondary analysis (the primary being the complete relief rates). In general, we should discourage this; however, given that this secondary analysis is traditionally the one we have been looking at (2-hr response rate), it seems reasonable to report it. We have done this in other triptans where the primary comparison was one against an active comparator, but we allowed reporting the results of the comparison with placebo.

Precautions: Pediatric Use

The sponsor proposes the following paragraph to be inserted after the first paragraph (which already does not recommend Maxalt in patients under 18 years of age).

The efficacy of Maxalt (5 mg) in patients aged 12 to 17 was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see Clinical Studies).

In order to maintain consistency with sumatriptan labeling, and eletriptan approvable labeling, I would recommend:



7. Recommendations

I recommend approval of the efficacy supplement, with the recommended changes in labeling as described above.

8. Addendum (6/20/00)

During the course of the review of this application, we decided not to include any biopharm data on adolescents, since the drug will not be indicated for that population. As a result, there is no biopharmaceutics review to this sNDA and my statements referring to the biopharm review should be ignored for this reason.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R. Levin

ao 2/24/00
cc:
HFD-120
NDA 20-864 SE5-02
electronic copy-Levin

APPEARS THIS WAY ON ORIGINAL

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20864 SE5-002(BL)**
Sponsor:	**Merck**
Drug:	**Maxalt**
Proposed Indication:	**migraine**
Material Submitted:	**Amendment to NDA Supplement**
Correspondence Date:	**5/5/00**
Date Received / Agency:	**5/8/00**
Date Review Completed	**5/17/00**
Reviewer:	**Armando Oliva, MD**

1. Introduction

This is a response to our fax, in which we propose changes to the draft Maxalt labeling describing the experience in adolescents.

In that fax, we proposed several changes, which I describe below:

- remove adolescent PK information
- remove negative efficacy results from the clinical studies section
- strengthen the precautions: pediatric use section

2. Response from Sponsor

In response, the sponsor proposes the following changes to their initial 10/26/99 draft labeling.

- They agree to drop the adolescent PK information from the clinical pharmacology section
- They continue to report the negative results of the adolescent efficacy study in the clinical studies section. Their argument is because naratriptan labeling contains such information (which I have verified to be true). The statement remains:

In a single study in adolescents (n= 291), [redacted]

- They agree to strengthen the precautions: pediatric use section to read the following:

Pediatric Use

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, MAXALT is not recommended for use in patients under 18 years of age.

The efficacy of MAXALT Tablets (5 mg) in patients aged 12 to 17 years was not established in a randomized placebo- controlled trial of 291 adolescent migraineurs (see Clinical Studies). Adverse events observed [redacted] *were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans*

includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long- term safety of rizatriptan in pediatric patients has not been studied.

3. Comments

I recommend we approve the sponsor's 5/5/00 draft labeling with the following change to the clinical studies section. The change reflected below is intended to make the description of the negative adolescent study conform more closely to the similar statement in the naratriptan approved labeling.

Sponsor proposes:
In a single study in adolescents (n= 291), [redacted]

[redacted]

Prior to issuing the approval letter, we should fax the following information to the sponsor.

Body of FAX:
We are prepared to recommend approval of your draft labeling submitted on 5/5/00 with the following minor editorial change to the clinical studies section. The change is proposed in order to more closely resemble the similar statement present in the clinical trials section of the currently approved naratriptan labeling.

You propose:
Sponsor's statement:
In a single study in adolescents (n= 291), [redacted]

[redacted]

In the absence of any communication from you in the very near future, we will proceed with an action letter.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. /S/

I agree with Dr. Oliva. The supplements can be approved with the labeling changes recommended by the sponsor with the changes described by Dr. Oliva.

ao 5/17/00
cc:
HFD-120
NDA 20864 SE5-002(BL)

APPEARS THIS WAY
ON ORIGINAL

NDA:	20-864 (SE1-002) & 20-865 (SE1-004)	MAY 9 2000
Name of Drug:	Rizatriptan Benzoate (MAXALT)	
Indication:	Migraine	
Sponsor:	Merck & Co., Inc.	
Documents Reviewed:	Volume 1 of 1	
Study Reviewed:	054	

1. BACKGROUND

The original NDA 20-864 that included rizatriptan benzoate tablet formulation (MAXALT) and wafer formulation (MAXALT-MLT) has been approved for the indication of acute migraine. A single Phase III study (Study 039) was included in the NDA application for rizatriptan wafer 5 mg and 10 mg. A second study (Study 049) with same design and endpoints as Study 039 had been conducted for rizatriptan wafer between May and December 1996. A supplement to NDA 20-865 submitted to the Agency dated January 18, 1999 to change the information in the labeling section using combining data from the two rizatriptan wafer studies (Studies 039 & 049). All those studies were based on data from adult patients only.

Based on the results from Study 054, the sponsor plans to add the information for adolescent use in the labeling section for both rizatriptan tablet and wafer formulations. The extent are:

- In a single study in adolescents (N=291), [redacted]

- The efficacy of MAXALT Tablets (5 mg) in patients aged 12 to 17 years was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see Clinical Studies). Adverse events observed [redacted] were similar in nature to those reported in clinical trial in adults.

This statistical review is to focus on the data from adolescent patients that collected in Study 054.

2. STUDY 054

2.1 Study Design

Study 054 was a randomized, double-blind, placebo-controlled, parallel-groups outpatient study to examine the safety, tolerability and efficacy of rizatriptan 5 mg for the acute treatment of migraine in adolescents aged between 12 and 17 with a history of migraine for the 6 months prior to study start.

headache using either "Moderate pain" or "Severe pain" were recruited. Responders to study treatment were defined as the adolescent patients whose headache severity improved to "No headache" at 2 hours after administering the first blinded treatment:

2.2 Efficacy Measures

2.2.1 Primary efficacy endpoint: The primary efficacy endpoint was pain free at 2 hours after the initial dose. Pain free was defined as a reduction of headache severity from moderate or severe headache at baseline to no headache.

2.2.2 Secondary efficacy endpoints: The secondary efficacy endpoints included: (1) pain free at 0.5, 1, 1.5, 3, 4 hours, (2) pain relief at 0.5, 1, 1.5, 2, 3, 4 hours, (3) functional disability and associated symptoms at 0.5, 1, 1.5, 2, 3, 4 hours, (4) need for additional analgesia/antiemetics, (5) headache recurrence, (6) pain relief posttreatment for recurrence, and (7) quality of life.

2.2.3 Recruitment and randomization: In the protocol, a total of 360 male and female outpatients who were suffering from moderate/severe migrainous headache patients were to randomize into either placebo or rizatriptan 5mg groups. It was expected to end up with 240 patients to complete the acute study, i.e. approximately 120 subjects for each group.

2.3 Efficacy Analysis

The primary efficacy analysis was planned to use logistic regression analysis. The model included the main factors for treatment and country. The interaction of two main factors and baseline severity were also assessed by the logistic regression models. The primary efficacy measure was reduction of headache severity from moderate/severe to no headache/mild pain at 2 hours after the initial dose (Yes/No).

The statistical comparisons were based upon logistic regression analysis. The model included the main factors for country and treatment. The interaction of treatment by country was tested at 0.10 level.

2.4 Subjects

Study 054 was a multi-center trial. A total of 19 centers in the US participated in the study. A total of 360 subjects, as planned in the protocol, had been randomized into placebo and rizatriptan treatment group.

Sixty-four patients who did not take drug and 7 patients discontinued the participation due to some reasons were excluded from efficacy analysis. Among those who had taken drug, there were 5 patients had baseline headache measure missing. It ended with data from a total of 291 patients for the efficacy analyses, 142 patients for placebo and 149 patients for Rizatriptan group.

A placebo, female Caucasian patient (ID #0273) who was 18 years old at the time of recruitment had been included in sponsor's efficacy analysis. This patient had moderate headache at the baseline. It would not make any significant impact on sample size and efficacy analysis with including this patients in the study. For the simplicity, this patient is included in the age category

report.

2.4.1 Patients characteristics:

The majority of subjects of Study 054 were Caucasian (92%). Subjects were stratified for age and gender at randomization. The characteristics of patients, based on the 291 patients, are presented in Table 1.

Table 1. Demographic Characteristics

	Riza-5mg (N=149)	Placebo (N=142)	Overall (N=291)	p-value
Gender				
Male	66 (44.0%)	69 (47.0%)	135 (46.0%)	.800
Female	83 (56.0%)	78 (53.0%)	161 (54.0%)	
Age (Years)				
12-14	81 (54.0%)	71 (50.0%)	152 (52.3%)	.456
15-17	68 (46.0%)	71 (50.0%)	139 (47.8%)	
Mean	14.3	14.5	14.4	
SD	1.6	1.8	1.7	
Medium	14.0	14.0	14.0	
Origin				
White	137 (92.0%)	132 (93.0%)	269 (92.4%)	.744
Non-White	12 (8.0%)	10 (7.0%)	22 (7.6%)	
Baseline Severity				
Moderate	94 (63.1%)	78 (54.9%)	172 (59.1%)	.157
Severe	55 (36.9%)	64 (45.1%)	119 (40.9%)	
Presence of Aura				
Without Aura	135 (91.0%)	133 (93.7%)	268 (92.1%)	.334
With Aura	14 (9.0%)	9 (6.3%)	23 (7.9%)	

2.5 Sponsor's efficacy results

2.5.1 Primary efficacy: The response rates at 2 hours after initial dose were 32.2% and 28.2% of patients on placebo and rizatriptan 5mg, respectively. Rizatriptan treatment group was not significantly superior to placebo (p=.474). Neither the effect of center nor the interaction of treatment by center was statistically significant. Overall, the treatment effects were not associated with study region, baseline headache severity, gender, race, and age. No interaction effects were significant.

2.5.2 Sponsor's secondary efficacy results: This review includes sponsor's major secondary efficacy results that adapted from the sNDA. Those secondary efficacy results are summarized as the followings:

treatment and baseline severity, are presented in Appendix 1.1. In overall, Rizatriptan 5mg and placebo groups had similar rates of pain free at different time points within 4 hours after the initial dose. With the consideration of baseline severity, the rates of pain free were also similar between two groups.

(II) Pain relief at time points 0.5, 1, 1.5, 2, 3, and 4 hours

Appendix 1.2 shows the rates of patients reporting pain relief at different time points within 4 hours after initial dosing, by treatment and baseline severity. The rizatriptan group only had significantly better pain relief rate at 3 hours after initial dose. Like the rates of pain free within 4 hours, the baseline severity did not show significant influence on the rates of pain relief between two groups with all the different time points.

(III) Patients with associated symptoms

The overall percentages of patients with migraine symptoms of photophobia, phonophobia, nausea, and vomiting were summarized in Appendix 1.3 for each treatment group within 4 hours after the initial dose.

For the symptoms of photophobia and vomiting, there were no significant difference between rizatriptan 5mg and placebo groups for all time points within 4 hours. For phonophobia, rizatriptan 5mg groups had significant less percentage of patients having the symptom at 0.5 and 4.0 hours postdose. For nausea, rizatriptan 5mg group had less percentage at 1.0 and 1.5 hours postdose.

Appendix 1.4 shows the figures of the percentages of patients having the associated symptoms within 4 hours postdose. It is clearly that any between-group difference of percentage of patients having associated symptom was not consistent over time.

(IV) Need for additional medication or second dose within 24 hours

The sponsor presented the Kaplan-Meier curves for time to additional migraine medication or second dose within 24 hours using. The figure in Appendix 1.5 shows that 46% of placebo patients had taken either additional medication over the 24-hour, compared to 39% of patients on Riza-5mg groups. Overall, the curves do not significantly from each other (p=0.125).

(V) Patients having recurrence within 24 hours after pain relief with the initial dose

Of the 177 patients who reported pain relief (either mild headache or no headache pain) at 2 hours postdose, the recurrence rates within 24 hours were 17.7% (N=14) and 11.2% (N=11) for placebo and rizatriptan 5mg groups, respectively. The 95% confidence interval for the recurrence rates are 10.0% to 27.9% and 5.7% to 19.2%, respectively.

(VI) pain relief posttreatment for recurrence

At 2 hours after the second dose, the rates of pain relief were 69.2% and 72.7% for placebo and rizatriptan 5mg groups, respectively. The 95% CI for the rates of pain relief post-treatment for recurrence are similarly, 38.6% to 90.9% and 39.0% to 94.0%. Both the recurrence rates within 24 hours after pain relief with the initial dose and rates of pain relief post-treatment for recurrence are summarized in Appendix 1.6.

In the sNDA, the sponsor also presented the results from the subgroup analysis for both pain free and pain relief at 2 hours after the initial dose (see Appendix 1.7 & Appendix 1.8). Analyses focused on the subgroups of location, baseline severity, gender, age, race, presence of aura, etc.

3. Reviewer's Analysis and Comments

3.1 Data for primary efficacy analysis

Based on the sponsor's data, those 291 patients that were identified to conduct the primary efficacy analysis (see Section 2.4) were adequate. However, the data that submitted to the Agency is not clean. Specifically, the time variable, PERIOD, for 17 subjects in the database had significant mistakes due to unknown reason, which may lead to the difficulty of identifying accurate endpoint for those 17 subjects.

3.2 Primary efficacy analysis

After deciding the most likely endpoint for those 17 subjects based on my best judgement, the primary efficacy analysis was conducted. The percentages of pain-free patients at 2 hour after initial dosing are 33.6% and 27.5% for rizatriptan 5mg group and placebo, respectively. The p-value obtained from a Chi-square test to test the significant difference between the two groups is .260 with one degree of freedom.

Study 054 was a multi-center trials and patients were recruited from 19 centers in the United States. With the concerns of small sample size for some centers and data, the by-site subgroup analysis may provide misleading information, Thus, no by-site subgroup analysis have been conducted.

3.3 Percentage of patients with associated symptoms within 4 hours after the initial dose among those who had the symptoms at the baseline

Similar "typo" problems occurred to data with the associated symptoms. As I did for the primary efficacy analysis, minor data have been cleaned based on my best judgement to conduct statistical analyses for the associated symptoms, nausea, photophobia and phonophobia.

The sponsor presented the percentage of patients with associated symptoms within 4 hours. Although the baseline severity between rizatriptan 5mg and placebo groups were similar, the longitudinal change of percentage of patients with associated symptoms among those had symptoms at the first migraine attack should be documented. Due to small number of patients reporting symptom of vomiting at baseline, the longitudinal change for symptoms of photophobia, phonophobia, and nausea are discussed in this review.

It shows that 117 and 106 patients of rizatriptan 5mg and placebo groups, respectively, had symptom of photophobia at the baseline; 104 and 96 patients of rizatriptan and placebo groups, respectively, had baseline phonophobia; and 60 and 70 patients of rizatriptan and placebo groups, respectively, had nausea symptom at baseline.

points with 4 hours among those who had the symptoms at baseline. The results show that the response rates between rizatriptan 5mg and placebo were not significantly different over time.

Table 3. Response Rates of Photophobia, Phonophobia, and Nausea within 4 Hours for Those Who Had the Symptoms at Baseline

	Rizatriptan 5mg	Placebo	p-value
Photophobia			
baseline	0.0% (0/117)	0.0% (0/106)	
0.5 hr	7.7% (9/117)	12.4% (13/105)	.243
1 hr	25.6% (30/117)	23.6% (25/106)	.722
1.5 hr	40.5% (47/116)	37.1% (39/105)	.607
2 hr	54.4% (62/114)	48.1% (50/104)	.352
3 hr	68.6% (70/102)	59.0% (56/95)	.157
4 hr	75.3% (67/89)	68.4% (54/79)	.318
Phonophobia			
baseline	0.0% (0/104)	0.0% (0/96)	
0.5 hr	16.4% (17/104)	25.0% (24/96)	.130
1 hr	35.6% (37/104)	35.4% (34/96)	.981
1.5 hr	51.5% (53/103)	47.4% (45/95)	.565
2 hr	62.7% (64/102)	59.6% (56/94)	.649
3 hr	75.8% (69/91)	65.5% (57/87)	.131
4 hr	87.2% (68/78)	69.2% (54/78)	.007
Nausea			
baseline	0.0% (0/60)	0.0% (0/106)	
0.5 hr	31.7% (19/60)	30.0% (21/70)	.837
1 hr	48.3% (29/60)	41.4% (29/70)	.430
1.5 hr	62.1% (36/58)	48.6% (34/70)	.127
2 hr	66.1% (37/56)	60.9% (42/69)	.549
3 hr	72.9% (35/48)	76.1% (51/67)	.697
4 hr	81.4% (35/43)	78.6% (44/56)	.729

4. Conclusion

Sponsor's clinical data does not demonstrate the superiority of using rizatriptan in the treatment of adolescents with acute migraine at different time points after initial dose.

/S/

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Archival of NDA #20-856/S-002 & S-004

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ON ORIGINAL

3. Efficacy (Cont.)

Table 18

Patients Reporting Pain-Free at Time Points Within 4 Hours
By Treatment and Baseline Severity

Treatment	Baseline Severity	N	0.5 hr			1.0 hr			1.5 hr			2.0 hr			3.0 hr			4.0 hr		
			n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Riza 5 mg	Moderate	94	0	0.0	0.0 to 3.1	9	9.6	4.5 to 17.4	22	23.4	15.3 to 33.3	37	39.4	29.4 to 50.0	53	56.4	45.8 to 66.6	66	70.2	59.9 to 79.2
	Severe	55	1	1.8	0.0 to 9.7	2	3.6	0.4 to 12.5	7	12.7	5.3 to 24.5	11	20.0	10.4 to 33.0	14	25.5	14.7 to 39.0	19	34.5	22.2 to 48.6
	Total	149	1	0.7	0.0 to 3.7	11	7.4	3.7 to 12.8	29	19.5	13.4 to 26.7	48	32.2	24.8 to 40.4	67	45.0	36.8 to 53.3	85	57.0	48.7 to 65.1
Placebo	Moderate	78	2	2.6	0.3 to 9.0	10	12.8	6.3 to 22.3	16	20.5	12.2 to 31.2	25	32.1	21.9 to 43.6	34	43.6	32.4 to 55.3	43	55.1	43.4 to 66.4
	Severe	64	0	0.0	0.0 to 4.6	2	3.1	0.4 to 10.8	5	7.8	2.6 to 17.3	15	23.4	13.8 to 35.7	17	26.6	16.3 to 39.1	28	43.8	31.4 to 56.7
	Total	142	2	1.4	0.2 to 5.0	12	8.5	4.4 to 14.3	21	14.8	9.4 to 21.7	40	28.2	20.9 to 36.3	51	35.9	28.0 to 44.4	71	50.0	41.5 to 58.5

No significant difference was observed between rizatriptan 5 mg and placebo at any time points.
(Pairwise comparisons performed for total patients only.)
N = Number of patients with nonmissing pain evaluations or carry-forward evaluations at 4 hours.
n (%) Number (percent) of patients with pain relief at indicated times.

Data Source: [4.7.1]

Appendix 1.1

Appendix 1.2

3. Efficacy (Cont.)

Table 23

Patients Reporting Pain Relief at Time Points Within 4 Hours
By Treatment and Baseline Severity

Treatment	Baseline Severity	N	0.5 hr			1.0 hr			1.5 hr			2.0 hr			3.0 hr			4.0 hr		
			n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Riza 5 mg	Moderate	94	15	16.0	9.2 to 25.0	41	43.6	33.4 to 54.2	65	69.1	58.8 to 78.3	70	74.5	64.4 to 82.9	80	85.1	76.3 to 91.6	82	87.2	78.8 to 93.2
	Severe	55	6	10.9	4.1 to 22.2	16	29.1	17.6 to 42.9	17	30.9	19.1 to 44.8	28	50.9	37.1 to 64.6	31	56.4	42.3 to 69.7	33	60.0	45.9 to 73.0
	Total	149	21	14.1	8.9 to 20.7	57	38.3	30.4 to 46.6	82	55.0	46.7 to 63.2	98	65.8	57.6 to 73.3	111	74.5*	66.7 to 81.3	115	77.2	69.6 to 83.7
Placebo	Moderate	78	21	26.9	17.5 to 38.2	36	46.2	34.8 to 57.8	45	57.7	46.0 to 68.8	47	60.3	48.5 to 71.2	51	65.4	53.8 to 75.8	59	75.6	64.6 to 84.7
	Severe	64	4	6.3	1.7 to 15.2	10	15.6	7.8 to 26.9	19	29.7	18.9 to 42.4	32	50.0	37.2 to 62.8	39	60.9	47.9 to 72.9	43	67.2	54.3 to 78.4
	Total	142	25	17.6	11.7 to 24.9	46	32.4	24.8 to 40.8	64	45.1	36.7 to 53.6	79	55.6	47.1 to 64.0	90	63.4	54.9 to 71.3	102	71.8	63.7 to 79.1

* P-values <0.05 when compared to placebo.
(Pairwise comparisons performed for total patients only.)
N = Number of patients with nonmissing pain evaluations or carry-forward evaluations at 4 hours.
n (%) Number (percent) of patients with pain relief at indicated times.

Data Source: [4.7.1]

3. Efficacy (Cont.)

Table 33

Number (%) of Patients Having Associated Symptoms by Treatment
(All-Patients-Treated)

Hour	Symptom	Riza 5 mg			Placebo		
		N	n	%	N	n	%
Baseline	Photophobia	149	117	(78.5%)	142	106	(74.6%)
	Phonophobia	149	104	(69.8%)	142	96	(67.6%)
	Nausea	149	60	(40.3%)	142	70	(49.3%)
	Vomiting	149	4	(2.7%)	142	7	(4.9%)
0.5 Hr	Photophobia	149	117	(78.5%)	142	100	(70.4%)
	Phonophobia	149	97	(65.1%)*	142	76	(53.5%)
	Nausea	149	52	(34.9%)	142	58	(40.8%)
	Vomiting	148	3	(2.0%)	142	7	(4.9%)
1.0 Hr	Photophobia	149	96	(64.4%)	142	90	(63.4%)
	Phonophobia	149	79	(53.0%)	142	72	(50.7%)
	Nausea	149	38	(25.5%)*	142	52	(36.6%)
	Vomiting	148	4	(2.7%)	142	4	(2.8%)
1.5 Hr	Photophobia	149	79	(53.0%)	142	74	(52.1%)
	Phonophobia	149	54	(36.2%)	142	57	(40.1%)
	Nausea	149	32	(21.5%)*	142	49	(34.5%)
	Vomiting	148	6	(4.1%)	142	2	(1.4%)
2.0 Hr	Photophobia	149	59	(39.6%)	142	62	(43.7%)
	Phonophobia	149	44	(29.5%)	142	44	(31.0%)
	Nausea	149	28	(18.8%)	142	39	(27.5%)
	Vomiting	149	4	(2.7%)	142	3	(2.1%)
3.0 Hr	Photophobia	149	45	(30.2%)	142	53	(37.3%)
	Phonophobia	149	32	(21.5%)	142	42	(29.6%)
	Nausea	149	25	(16.8%)	142	29	(20.4%)
	Vomiting	149	5	(3.4%)	142	7	(4.9%)
4.0 Hr	Photophobia	149	37	(24.8%)	142	45	(31.7%)
	Phonophobia	149	24	(16.1%)*	142	38	(26.8%)
	Nausea	149	20	(13.4%)	142	29	(20.4%)
	Vomiting	149	4	(2.7%)	142	3	(2.1%)

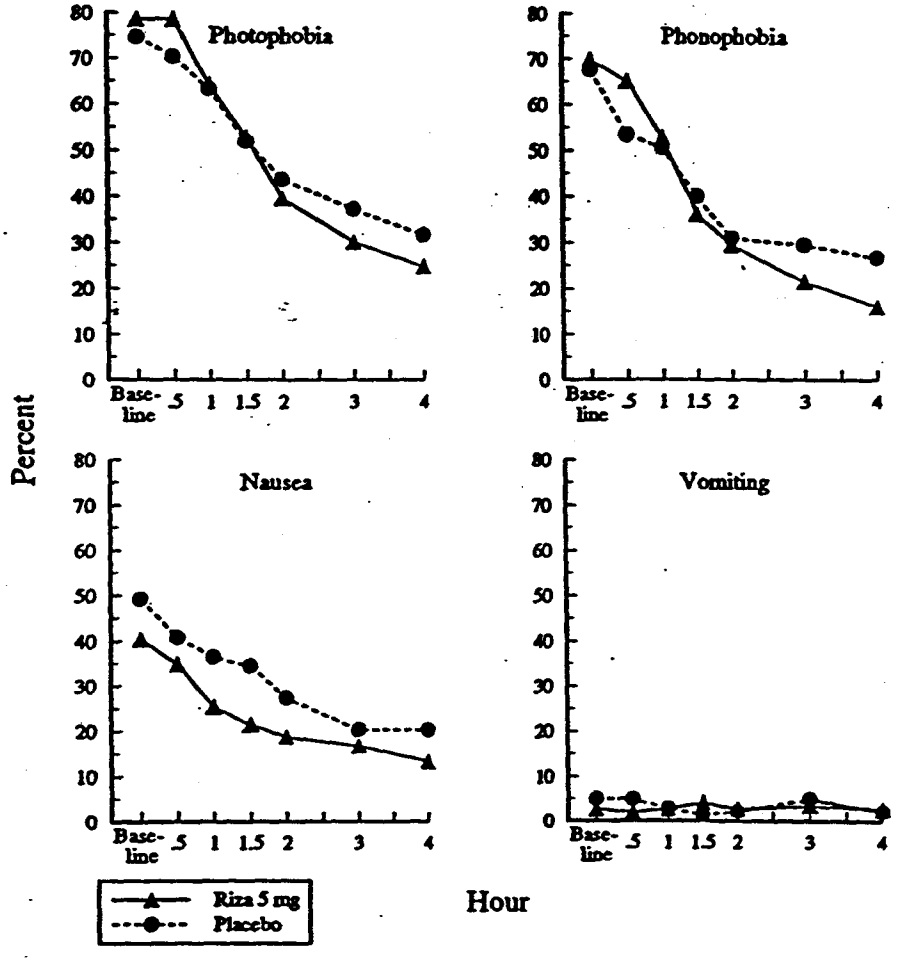
* P-values <0.05 when compared to placebo.

Data Source: [4.7.3]

3. Efficacy (Cont.)

Figure 5

Percentage of Patients Having Associated Symptoms
at 2 Hours by Treatment

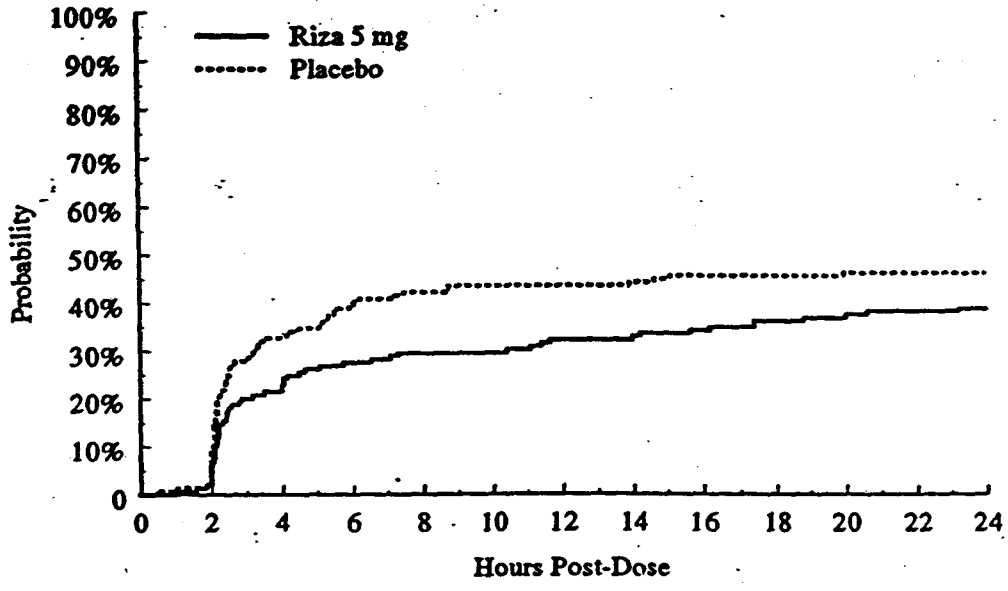


Data Source: [4.7.3]

3. Efficacy (Cont.)

Figure 6

Probability of Taking Additional Migraine Medication
or Second Dose of Test Medication Within 24 Hours Postdose



Data Source: [4.3]

3. Efficacy (Cont.)

Table 29

Patients Having Recurrence Within 24 Hours by Treatment
(All-Patients-Treated)

Treatment	R	n	%	95% CI
Riza 5 mg	98	11	11.2	5.7 to 19.2
Placebo	79	14	17.7	10.0 to 27.9
R = Number of patients who had relief at 2 hours after the initial dose.				
n = Number of patients who had recurrence within 24 hours of initial dose.				

Data Source: [4.7.4]

Table 30

Patients Reporting Pain Relief 2 Hours After Treatment
of (First) Recurrence by Treatment
(All-Patients-Treated)

Treatment	Time	U	n	%	95% CI
Riza 5 mg	2.0 hours	11	8	72.7	39.0 to 94.0
Placebo†	2.0 hours	13	9	69.2	38.6 to 90.9
U Number of patients who had recurrence within 24 hours of initial dosing.					
n: Patients who had pain relief after treating the recurrence at 2 hours after the second dose.					
† One patient (AN 0024, Study Number 054-002), who took the second dose of study medication, did not record in the diary any headache ratings at baseline or at 2 hours after treatment of first recurrence.					

Data Source: [4.7.4]

3. Efficacy (Cont.)

Table 16

Percent of Patients Pain-Free 2 Hours Postdose
by Patient Demographics

	Riza 5 mg			Placebo		
Demographic Variable	N	n	%	N	n	%
Study Region						
North East	31	9	29.0	31	8	25.8
South East	35	14	40.0	32	7	21.9
Mid-West	46	13	28.3	46	15	32.6
South	37	12	32.4	33	10	30.3
Baseline Severity						
Moderate	94	37	39.4	78	25	32.1
Severe	55	11	20.0	64	15	23.4
Gender						
Male	66	22	33.3	65	20	30.8
Female	83	26	31.3	77	20	26.0
Age						
12 to 14	81	30	37.0	71	18	25.4
15 to 17†	68	18	26.5	71	22	31.0
Race						
Non-White	12	4	33.3	10	2	20.0
White	137	44	32.1	132	38	28.8
Aura						
Without	135	47	34.8	133	37	27.8
With	14	1	7.1	9	3	33.3
Prophylactic Use						
No prophylaxis	133	43	32.3	137	39	28.5
Any prophylaxis	16	5	31.3	5	1	20.0
β-blockers	1	0	0.0	1	0	0.0
Ca channel blockers	1	1	100.0	0	0	0.0
SSRI	13	4	30.8	4	1	25.0
Tricyclic antidepressant	4	2	50.0	0	0	0.0
Valproate	1	1	100.0	0	0	0.0
Oral Contraceptives Use						
No	147	47	32.0	134	38	28.4
Yes	2	1	50.0	8	2	25.0

† The 18-year-old patient was included in the 15- to 17-year-old age group for simplicity.

Data Source: [4.2; 4.3; 4.7.1]

3. Efficacy (Cont.)

Table 21

Percent of Patients With Pain Relief 2 Hours Postdose
by Patient Demographics

Demographic Factors	Riza 5 mg			Placebo		
	N	n	%	N	n	%
Region						
NE	31	22	71.0	31	16	51.6
SE	35	25	71.4	32	18	56.3
MW	46	33	71.7	46	25	54.3
S	37	18	48.6	33	20	60.6
Baseline Severity						
Moderate	94	70	74.5	78	47	60.3
Severe	55	28	50.9	64	32	50.0
Gender						
Male	66	44	66.7	65	38	58.5
Female	83	54	65.1	77	41	53.2
Age						
12 to 14	81	58	71.6	71	38	53.5
15 to 17†	68	40	58.8	71	41	57.7
Race						
Non-White	12	8	66.7	10	5	50.0
White	137	90	65.7	132	74	56.1
Aura						
With	14	9	64.3	9	5	55.6
Without	135	89	65.9	133	74	55.6
Prophylactic Use						
No prophylaxis	133	89	66.9	137	78	56.9
Any prophylaxis	16	9	56.3	5	1	20.0
β-blockers	1	0	0.0	1	0	0.0
Ca channel blockers	1	1	100.0	0	0	0.0
SSRI	13	8	61.5	4	1	25.0
Tricyclic antidepressant	4	3	75.0	0	0	0.0
Valproate	1	1	100.0	0	0	0.0
Oral Contraceptives Use						
No	147	97	66.0	134	76	56.7
Yes	2	1	50.0	8	3	37.5

† The 18-year-old patient was included in the 15- to 17-year-old age group for simplicity.

Data Source: [4.2; 4.3; 4.7.1]

MEMORANDUM OF TELEPHONE CONVERSATION
IND 40,458 (SN 208)
NDAs 20-864, 20-865

Drug:	Rizatriptan (Maxalt)
Sponsor:	Merck
Date:	April 17, 2000
Conversation Between:	Agency: L Chen, PM Firm: C. Sanders, MD
Telephone #:	610.397.2850
Purpose:	

The Agency requested this teleconference to inform the Firm that their "Proposed Pediatric Study Request" submitted October 7, 1999 had been discussed further internally, including input from the Pediatric Implementation Team (PdIT) obtained on April 5, 2000. The study(ies) in adolescents for migraine submitted by the Sponsor thus far have been negative. The Division would ordinarily require an efficacy study, pharmacokinetic study and long term safety study in the Written Request. If the Sponsor would agree to do further efficacy study(ies) that showed positive results, the Division would be likely to issue a Written Request for the remaining pharmacokinetic and long term safety studies.

The Firm indicated their need for internal discussion, and that a response would be communicated to the Agency shortly.

/S/
Lana Chen, R.Ph.

cc: Orig IND 40,458
NDAs 20-864, 20-865
HFD-120
HFD-120/Katz
/Levin/Feeney/Oliva
/Chen

Final: 4/17/00

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MERCK & CO., INC.
West Point, PA 19486, USA

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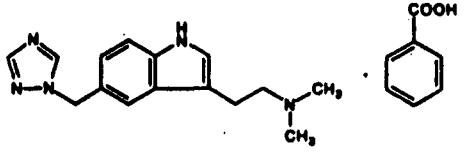
MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT™
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

MAXALT* contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

MAXALT Tablets and MAXALT-MLT** Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive

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ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} receptors. Rizatriptan has weak affinity for other 5-HT_1 receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT_7 receptor, but has no significant activity at 5-HT_2, 5-HT_3, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-$HT_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets, but the rate of absorption is somewhat slower with MAXALT-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

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The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-$HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-$HT_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

1. Biopharm Ref. P048: p. 38
2. Biopharm Ref. P048: p. 41

Elderly: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in

healthy subjects. In hemodialysis patients, (creatinine clearance < 2 mL/min/1.73 m²), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions (See also PRECAUTIONS, *Drug Interactions.*)

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when MAXALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions.*)

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS; DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of MAXALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

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Clinical Studies

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 1.

Table 1
Response Rates 2 Hours Following Treatment of Initial Headache

Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

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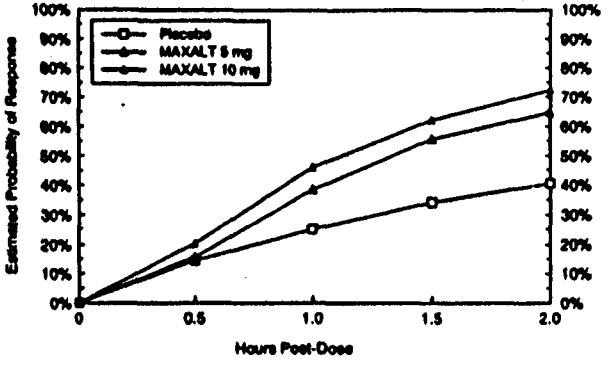
The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours††



†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment†††

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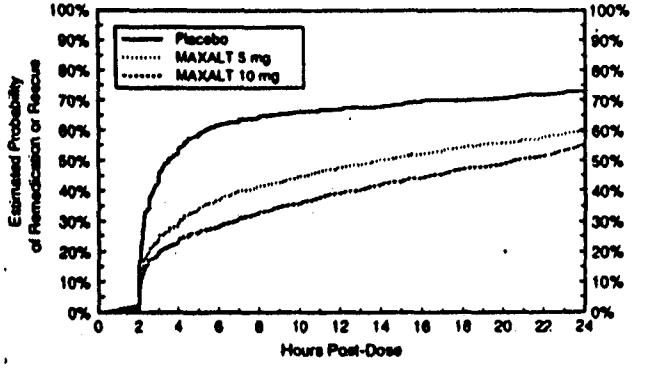

††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

In a single study in adolescents (n=291)

3. Clinical Ref. P054: p. 65

MAXALT-MLT Orally Disintegrating Tablets

The efficacy of MAXALT-MLT 5 mg and 10 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT-MLT were approximately 66% in either the MAXALT-MLT 5 mg and 10 mg groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT-MLT is depicted in Figure 3.

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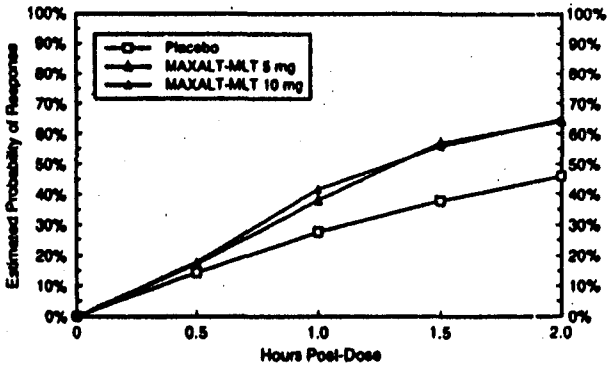
Figure 3: Estimated Probability of Achieving an Initial Headache Response with MAXALT-MLT by 2 Hours‡



‡ Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 4.

Figure 4: Estimated Probability of Patients Taking a Second Dose of MAXALT-MLT or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment‡‡

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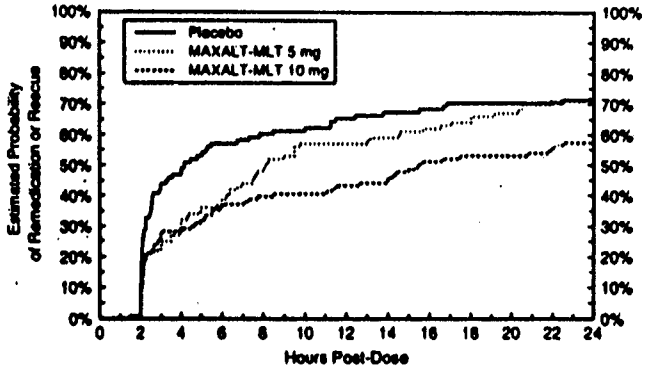

‡‡ In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

INDICATIONS AND USAGE

MAXALT is indicated for the acute treatment of migraine attacks with or without aura in adults.

MAXALT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of MAXALT has not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

MAXALT should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because MAXALT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

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MAXALT should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

MAXALT is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

WARNINGS

MAXALT should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: **Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, rizatriptan should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration

of the first dose of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received rizatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of MAXALT and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use MAXALT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to rizatriptan.

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT$_1$ agonists. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low. Among the 3700 patients with migraine who participated in premarketing clinical trials of MAXALT, one patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Cerebrovascular Events and Fatalities Associated with 5-HT$_1$ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT$_1$ agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT$_1$ agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT$_1$ agonists with and without a history of hypertension. In healthy young male and female subjects who received

maximal doses of MAXALT (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with MAXALT in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischemic ECG changes in clinical trials (one patient experienced chest pain with possible ischemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see CLINICAL PHARMACOLOGY, *Special Populations*).

Renally Impaired Patients: Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan (see CLINICAL PHARMACOLOGY, *Special Populations*).

Hepatically Impaired Patients: Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see CLINICAL PHARMACOLOGY, *Special Populations*).

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

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Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT-MLT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 5-mg orally disintegrating tablet contains 1.05 mg phenylalanine, and each 10-mg orally disintegrating tablet contains 2.10 mg phenylalanine.

Information for Patients

Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness has also been reported in some patients receiving MAXALT. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of MAXALT.

Physicians should instruct their patients to read the patient package insert before taking MAXALT. See the accompanying PATIENT INFORMATION leaflet.

MAXALT-MLT Orally Disintegrating Tablets

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT.

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions*.)

Propranolol: Rizatriptan 5 mg should be used in patients taking propranolol, as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70% (see CLINICAL PHARMACOLOGY, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Other 5-HT$_1$ agonists: The administration of rizatriptan with other 5-HT$_1$ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT$_1$ agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with rizatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. No clinical or pharmacokinetic interactions were observed when MAXALT 10 mg was administered with paroxetine.

Monoamine oxidase inhibitors: Rizatriptan should not be administered to patients taking MAO-A inhibitors and non-selective MAO inhibitors; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of rizatriptan and its metabolite (see CLINICAL PHARMACOLOGY, *Drug Interactions*; CONTRAINDICATIONS).

Drug/Laboratory Test Interactions

MAXALT is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The lifetime carcinogenic potential of rizatriptan was evaluated in a 100-week study in mice and a 106-week study in rats at oral gavage doses of up to 125 mg/kg/day. Exposure data were not obtained in those studies, but plasma AUC's of parent drug measured in other studies after 5 and 21 weeks of oral dosing in mice and rats, respectively, indicate that the exposures to parent drug at the highest dose level in the carcinogenicity studies would have been approximately 150 times (mice) and 240 times (rats) average AUC's measured in humans after three 10 mg doses, the maximum recommended total daily dose. There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis: Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, the *in vitro* mammalian cell mutagenesis assay in V-79

Chinese hamster lung cells, the *in vitro* alkaline elution assay in rat hepatocytes, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* chromosomal aberration assay in mouse bone marrow.

Impairment of Fertility: In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 225 times the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

Pregnancy: Pregnancy Category C

In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation with doses of 10 and 100 mg/kg/day. Maternal plasma drug exposures (AUC) at these doses were approximately 15 and 225 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The effects on offspring growth occurred in the absence of any apparent maternal toxicity in this study. The developmental no-effect dose was 2 mg/kg/day (maternal exposure approximately 1.5 times human exposure at the MRDD). The full spectrum of developmental toxicity is not known because adequately high doses, i.e., those producing some maternal toxicity, were not evaluated in the reproduction study. When higher, maternally toxic doses (250 mg/kg/day or greater) were evaluated over the same period of development in a rat dose range-finding study, pup mortality was increased.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses of 100 and 50 mg/kg/day, respectively, during organogenesis. Fetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses (maternal exposures approximately 225 and 115 times the human exposure at the MRDD in rats and rabbits, respectively). The developmental no-effect dose in these studies was 10 mg/kg/day in both rats and rabbits (maternal exposures approximately 15 times human exposure at the MRDD). Toxicokinetic studies demonstrated placental transfer of drug in both species.

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There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to MAXALT while pregnant. Healthcare providers are encouraged to report any prenatal exposure to MAXALT by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

It is not known whether this drug 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. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatric Use

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, MAXALT is not recommended for use in patients under 18 years of age.

The efficacy of MAXALT Tablets (5 mg) in patients aged 12 to 17 years was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see *Clinical Studies*).[4] Adverse events observed ——— were similar in nature to those reported in clinical trials in adults.[5]

4. Clinical Ref. P054: p. 65
5. Clinical Ref. P054: p. 131

Use in the Elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with MAXALT is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n=17).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

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Incidence in Controlled Clinical Trials: Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT Tablets. The most common adverse events during treatment with MAXALT were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Table 2 lists the adverse events regardless of drug relationship (incidence ≥ 2% and greater than placebo) after a single dose of MAXALT. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2
Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences
After a Single Dose of MAXALT Tablets or Placebo

	% of Patients		
Adverse Experiences	MAXALT 5 mg (N=977)	MAXALT 10 mg (N=1167)	Placebo (N=627)
Atypical Sensations	4	5	4
Paresthesia	3	4	<2
Pain and other Pressure Sensations	6	9	3
Chest Pain: tightness/pressure and/or heaviness	<2	3	1
Neck/throat/jaw: pain/tightness/pressure	<2	2	1
Regional Pain: tightness/pressure/heaviness	<1	2	0
Pain, location unspecified	3	3	<2
Digestive	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
Neurological	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4

Other			
Asthenia/fatigue	4	7	2

MAXALT was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of MAXALT: In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT (N=3716) and reported an event divided by the total number of patients exposed to MAXALT. All reported events are included, except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least (>)1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

General: Infrequent were chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. Rare were fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: Frequent were warm/cold sensations.

Cardiovascular: Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare was angina pectoris.

Digestive: Frequent were diarrhea and vomiting. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: Infrequent was dehydration.

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Musculoskeletal: Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: Frequent were hypesthesia, mental acuity decreased, euphoria and tremor. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. Rare were: dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: Frequent was dyspnea. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: Frequent was flushing. Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital system: Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

The adverse experience profile seen with MAXALT-MLT Orally Disintegrating Tablets was similar to that seen with MAXALT Tablets.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of MAXALT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

No overdoses of MAXALT were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

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In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5 and 10 mg of MAXALT Tablets or MAXALT-MLT were effective for the acute treatment of migraines in adults. There is evidence that the 10-mg dose may provide a greater effect than the 5-mg dose (see *Clinical Studies*). Individuals may vary in response to doses of MAXALT Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10-mg dose with the potential risk for increased adverse events.

Redosing: Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Patients receiving propranolol: In patients receiving propranolol, the 5-mg dose of MAXALT should be used, up to a maximum of 3 doses in any 24-hour period. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.)

For MAXALT-MLT Orally Disintegrating Tablets, administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister within an outer aluminum

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pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

HOW SUPPLIED

No. 3732 — MAXALT Tablets, 5 mg, are pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other. They are supplied as follows:

NDC 0006-0266-06, unit of use carrying case of 6 tablets.

No. 3733 — MAXALT Tablets, 10 mg, are pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other. They are supplied as follows:

NDC 0006-0267-06, unit of use carrying case of 6 tablets.

No. 3800 — MAXALT-MLT Orally Disintegrating Tablets, 5 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified triangle on one side, and measuring 10.0-11.5 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3800-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

No. 3801 — MAXALT-MLT Orally Disintegrating Tablets, 10 mg, are white to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side, and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows:

NDC 0006-3801-06, 2 x unit of use carrying case of 3 orally disintegrating tablets (6 tablets total).

Storage

Store MAXALT Tablets at room temperature, 15-30°C (59-86°F). Dispense in a tight container, if product is subdivided.

Store MAXALT-MLT Orally Disintegrating Tablets at room temperature, 15-30°C (59-86°F). The patient should be instructed not to remove the blister from the outer aluminum pouch until the patient is ready to consume the orally disintegrating tablet inside.

CURRENT CIRCULAR SHOWING REVISIONS

COMMENTS/SUPPORT

MAXALT® (Rizatriptan Benzoate) Tablets
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MAXALT Tablets are manufactured for:
MERCK & CO., INC., West Point, PA 19486, USA
By:
MSD, Ltd. Cramlington
Northumberland, NE23 9JU, UK

MAXALT-MLT Orally Disintegrating Tablets are manufactured for:
MERCK & CO., INC., West Point, PA 19486, USA
By:
Scherer DDS, Ltd.
Swindon, Wiltshire, SN5 8RU, UK

Issued ~~October 1998~~
Printed in USA

constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of MAXALT Tablets and MAXALT-MLT Orally Disintegrating Tablets, but the rate of absorption is somewhat slower with MAXALT-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-$HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-$HT_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

Elderly: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients, (creatinine clearance < 2 mL/min/1.73 m^2), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions (See also PRECAUTIONS, *Drug Interactions*.)

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when MAXALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions*.)

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS; DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of MAXALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Clinical Studies

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 1.

Table 1
Response Rates 2 Hours Following Treatment of Initial Headache

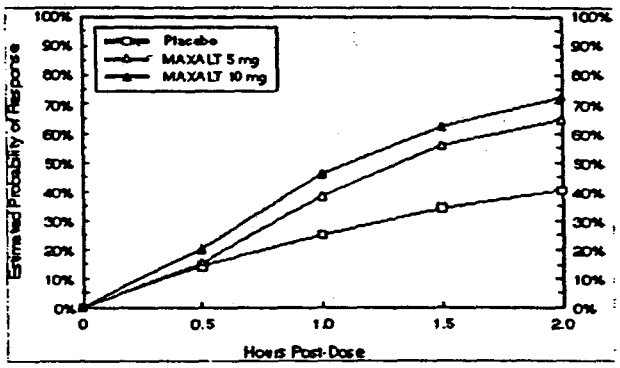
Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours††



†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment†††