

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-864/S-008 & 20-865/S-009

Trade Name: Maxalt Tablets and
Maxalt-MLT Orally Disintegrating Tablets

Generic Name: rizatriptan benzoate

Sponsor: Merck & Co., Inc.

Approval Date: 04/22/2002

Indications: For the acute treatment of migraine attacks with or without aura in adults.

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 20-864/S-008

NDA 20-865/S-009

Merck Research Laboratories
A Division of Merck & Co., Inc.
Attention: Charlene G. Sanders, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, GL A-20
West Point, PA 19486

Dear Dr. Sanders:

Please refer to your supplemental new drug applications dated May 4, 2001, received May 7, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MAXALT™ (rizatriptan benzoate) Tablets and MAXALT-MLT™ (rizatriptan benzoate) Orally Disintegrating Tablets.

These "Changes Being Effected" supplemental new drug applications provide for revisions to ADVERSE REACTION, *Post-Marketing Experience* section. Specifically, the terms "angioedema" and "wheezing" are included under a new subheading titled, "General: Hypersensitivity" and the term "Toxic Epidermal Necrolysis (TEN)" has been relocated to this section. Additionally, the Patient Package Insert (PPI) has been updated to reflect the changes to the package insert. Lastly, the company address has been revised to indicate the worldwide headquarters location of Merck & Co., Inc.

We have completed the review of these supplemental applications. They are approved effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on May 4, 2001.

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

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

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

NDA 20-864/S-008

NDA 20-865/S-009

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
4/22/02 09:06:06 AM

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NDA 20-864/S-008 & 20-865/S-009

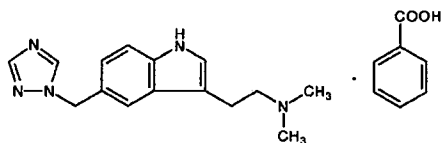
LABELING

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 C₁₅H₁₉N₅•C₇H₆O₂, 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-HT₁ receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT₇ receptor, but has no significant activity at 5-HT₂, 5-HT₃, 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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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 ¹⁴C-rizatriptan. Following oral administration of ¹⁴C-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 (K_i =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 m²), 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.

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

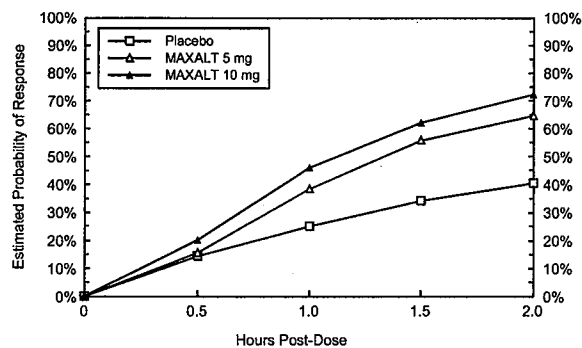
† Results for initial headache only.

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††

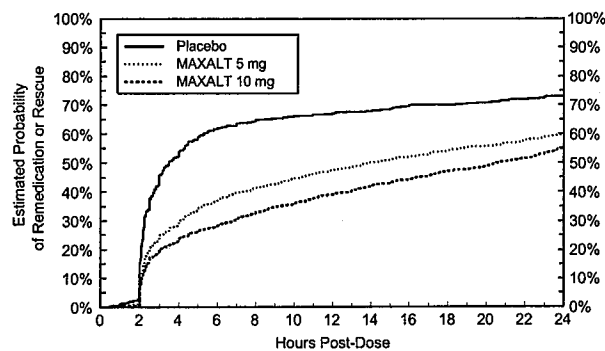


†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 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. In two additional similar studies, efficacy was unaffected by relationship to menses. 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 was established in two multicenter, randomized, placebo-controlled trials that were similar in design to the trials of MAXALT Tablets. Patients were instructed to treat a moderate to severe headache. Patients treated in these studies were primarily female (88%) and Caucasian (95%), with a mean age of 42 years (range 18-72).

In both studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT-MLT 5 or 10 mg compared to those who received placebo. The results from the 2 controlled studies using the marketed formulation are summarized in Table 2.

Table 2
Response Rates 2 Hours Following Treatment of Initial Headache

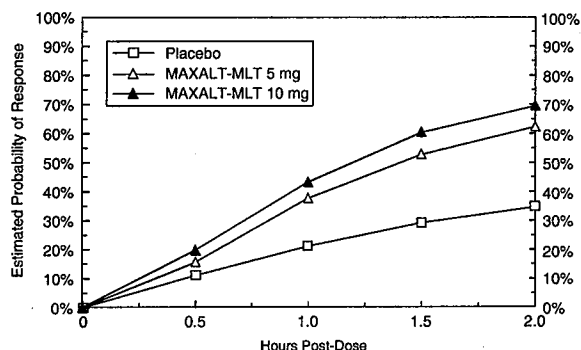
Study	Placebo	MAXALT-MLT 5 mg	MAXALT-MLT 10 mg
1	47% (n=98)	66%* (n=100)	66%* (n=113)
2	28% (n=180)	59%* (n=181)	74%*. ** (n=186)

* p value < 0.01 in comparison with placebo

** p value < 0.01 in comparison with 5 mg

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†

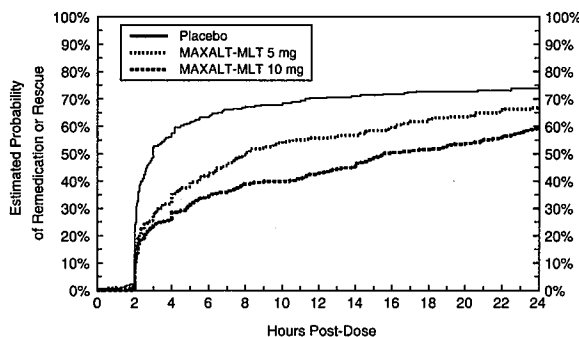


† Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. The averages displayed are based on pooled data from 2 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1 and 2). 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††



†† This Kaplan-Meier plot is based on data obtained in 2 placebo-controlled outpatient clinical trials (Studies 1 and 2). 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 have 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-HT₁ 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-HT₁ Agonists: Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following the administration of rizatriptan. Life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of other 5-HT₁ agonists. Considering the extent of use of 5-HT₁ agonists in patients with migraine, the incidence of these events is extremely low. MAXALT can cause coronary vasospasm. Because of the close proximity of the events to MAXALT use, a causal relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing experience with rizatriptan: 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.

Postmarketing experience with rizatriptan: Serious cardiovascular events have been reported in association with the use of MAXALT. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by rizatriptan or to reliably assess causation in individual cases.

Cerebrovascular Events and Fatalities Associated with 5-HT₁ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT₁ 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-HT₁ 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-HT₁ agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT₁ 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-HT₁ 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-HT₁ 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-HT₁ agonists: The administration of rizatriptan with other 5-HT₁ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT₁ 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-HT₁ 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 general reproductive 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 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. In a pre- and post-natal developmental toxicity study in rats, an increase in mortality of the offspring at birth and for the first three days after birth, a decrease in pre- and post-weaning weight gain, and decreased performance in a passive avoidance test (which indicates a decrease in learning capacity of the offspring) were observed at doses of 100 and 250 mg/kg/day. The no-effect dose for all of these effects was 5 mg/kg/day, approximately 7.5 times the exposure in humans receiving the MRDD. With doses of 100 and 250 mg/kg/day, the decreases in average weight of both the male and female offspring persisted into adulthood. All of these effects on the offspring in both reproductive toxicity studies occurred in the absence of any apparent maternal toxicity.

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.

Geriatric Use

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-HT₁ 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 3 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 3
 Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences
 After a Single Dose of MAXALT Tablets or Placebo

Adverse Experiences	% of Patients		
	MAXALT 5 mg (N=977)	MAXALT 10 mg (N=1167)	Placebo (N=627)
<i>Atypical Sensations</i>	4	5	4
Paresthesia	3	4	<2
<i>Pain and other Pressure Sensations</i>	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
<i>Digestive</i>	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
<i>Neurological</i>	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4
<i>Other</i>			
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.

Postmarketing Experience

The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and non-domestic use of rizatriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of rizatriptan in their causation cannot be reliably determined.

Cardiovascular: Myocardial ischemia, Myocardial infarction (see WARNINGS).

Cerebrovascular: Stroke.

Special Senses: Dysgeusia.

General: *Hypersensitivity:* angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, toxic epidermal necrolysis.

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 PHARMACOLOGY, *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.

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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.**, Whitehouse Station, NJ 08889, USA

By:

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

MAXALT-MLT Orally Disintegrating Tablets are manufactured for:

 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

By:

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

Issued December 2000

Printed in USA

Patient Information about
MAXALT® (max-awlt) and MAXALT-MLT®
for Migraine

Generic name: rizatriptan benzoate

Please read this information before you start taking MAXALT*. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss MAXALT when you start taking your medication and at regular checkups.

What is MAXALT and what is it used for?

MAXALT is a medication used for the treatment of migraine attacks in adults. MAXALT is a member of a class of drugs called selective 5-HT_{1B/1D} receptor agonists.

It is available as a traditional tablet (MAXALT) and as an orally disintegrating tablet (MAXALT-MLT*). Unless otherwise stated, the information contained in this leaflet applies both to MAXALT Tablets and to MAXALT-MLT Orally Disintegrating Tablets.

Tell your doctor about your symptoms. Your doctor will decide if you have migraine. Use MAXALT only for a migraine attack. MAXALT should not be used to treat headaches that might be caused by other, more serious conditions.

You will find more information about migraine at the end of this leaflet.

How should I take MAXALT?

Your doctor has prescribed either a 5 mg or 10 mg dosage of MAXALT or MAXALT-MLT for your migraine attack. When you have a migraine headache, take your medication as directed by your doctor.

MAXALT Tablets

If you are using MAXALT Tablets, swallow the tablet whole with liquid.

MAXALT-MLT Orally Disintegrating Tablets

If you are using MAXALT-MLT, leave the orally disintegrating tablet in its package until you are ready to take it. Remove the blister from the foil pouch. Do not push the tablet through the blister; rather, peel open the blister pack with dry hands and place the tablet on your tongue. The tablet will dissolve rapidly and be swallowed with your saliva. No liquid is needed to take the orally disintegrating tablet.

If your headache comes back after your initial dose, a second dose may be taken anytime after 2 hours of administering the first dose. For any attack where you have no response to the first dose, do not take a second dose without first consulting with your doctor. Do not take more than 30 mg

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of MAXALT in a 24-hour period, (for example, do not take more than three 10-mg tablets in a 24-hour period).

If you are receiving propranolol, you should use the 5-mg dose of MAXALT or MAXALT-MLT, up to a maximum of 3 doses (15 mg total) in a 24-hour period.

If your condition worsens, seek medical attention.

Who should not take MAXALT?

Do not take MAXALT if you:

- have had a serious allergic reaction to MAXALT or any of its ingredients
- have uncontrolled high blood pressure
- have heart disease or history of heart disease
- are currently taking monoamine oxidase (MAO) inhibitors** such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®) for mental depression, or have taken MAO inhibitors within the last two weeks.

MAXALT should not be used within 24 hours of treatment with another 5-HT₁ agonist** such as sumatriptan (IMITREX®), naratriptan (AMERGE™) or zolmitriptan (ZOMIG™); or ergotamine-type medications such as ergotamine (BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®), dihydro-ergotamine (D.H.E. 45®), or methysergide (SANSERT®).

What should I tell my doctor before and during treatment with MAXALT?

Tell your doctor:

- about any past or present medical problems
- about any history of high blood pressure, chest pain, shortness of breath, heart disease, or stroke
- about any risk factors for heart disease or blood vessel disease
 - high blood pressure or diabetes
 - high cholesterol
 - obesity
 - smoking
 - family history of heart disease or blood vessel disease
 - post menopausal
 - male over 40
- about any allergies you have or have had
- if you are pregnant or plan to become pregnant
- if you are breast-feeding or plan to breast-feed

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- about all drugs you are taking or plan to take, including those obtained without a prescription, and those you normally take for a migraine.

What if I am pregnant?

Do not use MAXALT if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

Can I take MAXALT with other medications?**

Do not take MAXALT with any other drug in the same class within 24 hours, such as sumatriptan (IMITREX®), naratriptan (AMERGE™) or zolmitriptan (ZOMIG™).

Do not take MAXALT within 24 hours of taking ergotamine-type medications such as ergotamine (BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®), dihydro-ergotamine (D.H.E. 45®) or methysergide (SANSERT®) to treat your migraine.

Do not take MAXALT when you are taking monoamine oxidase (MAO) inhibitors, such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®) for mental depression, or if it has been less than two weeks since you stopped taking an MAO inhibitor.

Ask your doctor for instructions about taking MAXALT if you are now taking propranolol (INDERAL®). (See **How should I take MAXALT?** section.)

What are the possible side effects of MAXALT?

Like all prescription drugs, MAXALT can cause side effects. In studies, MAXALT was generally well-tolerated. The side effects were usually mild and temporary. The following is **not** a complete list of side effects reported with MAXALT. Do not rely on this leaflet alone for information about side effects. Ask your doctor to discuss with you the more complete list of side effects.

In studies, the **most common** side effects reported were:

- **dizziness,**
- **sleepiness, tiredness, fatigue**
- **pain or pressure sensation (e.g., in the chest or throat)**

If you experience dizziness, sleepiness, tiredness or fatigue, you should evaluate your ability to perform complex tasks such as driving or operating heavy machinery.

Other, **less common** side effects reported in studies or general use were related to the:

Heart and blood vessels - Alterations in heartbeat, increased blood pressure and cold extremities.

Muscles - Muscle weakness, stiffness, and spasm; and muscle and bone pain.

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Nervous system - Nervousness, decreased mental sharpness, tremor, headache, abnormal sensation, vertigo, sleep disturbance, mood and personality changes, alterations in speech and movement, memory impairment, confusion and dream abnormality.

Digestive system - Stomach upset, diarrhea, dry mouth, constipation, gas, thirst, acid reflux, difficulty swallowing, changes in appetite, burping and inability of the tongue to move.

Skin - Flushing (redness of the face lasting a short time), hot flashes, sweating, itching, rash, acne and skin reaction to sunlight.

Respiratory - Difficult or rapid breathing, dryness or discomfort of the throat or nose, nose bleed, yawning and sinus disorder, cold-like symptoms, cough, and hiccups.

Special Senses - Visual disturbances, ringing in the ears, ear pain, eye discomfort, swelling or tearing, alterations in hearing and smelling, visual intolerance to light, and bad taste.

Miscellaneous - Allergic reactions including swelling of face, lips, tongue and/or throat which may cause difficulty in breathing and/or swallowing, wheezing, hives, rash, and severe sloughing of the skin. Also chills, heat sensitivity, swelling, bloating, hangover effect, fever, fainting, dizziness on standing up, warm/cold sensations, dehydration and changes in urination and menstruation.

As with other drugs in this class, there have been very rare reports of heart attack and stroke generally occurring in patients with risk factors for heart and blood vessel disease (see **What should I tell my doctor before and during treatment with MAXALT?**).

Tell your doctor about these or any other symptoms. If the symptoms persist or worsen, seek medical attention promptly. In addition, tell your doctor if you experience any symptoms that suggest an allergic reaction (See **Miscellaneous** above) after taking MAXALT.

What should I do if I take an overdose?

If you take more medication than you have been told to take, you should contact your doctor, hospital emergency department, or nearest poison control center immediately.

What is migraine and how does it differ from other headaches?

Migraine is an intense, throbbing, typically one-sided headache that often includes nausea, vomiting, sensitivity to light, and sensitivity to sound. According to many migraine sufferers, the pain and symptoms from a migraine headache are more intense than the pain and symptoms of a common headache.

Some people may have visual symptoms before the headache, such as flashing lights or wavy lines, called an aura.

Migraine attacks typically last for hours or, rarely, for more than a day, and they can return frequently. The severity and frequency of migraine attacks may vary.

Based on your symptoms, your doctor will decide whether you have migraine.

Who gets migraine?

Migraine headaches tend to occur in members of the same family. Both men and women get migraine, but it is more common in women.

What may trigger a migraine attack?

Certain things are thought to trigger migraine attacks in some people. Some of these triggers are:

- certain foods or beverages (e.g., cheese, chocolate, citrus fruit, caffeine, alcohol)
- stress
- change in a behavior (e.g., under/oversleeping; missing a meal; change in diet)
- hormonal changes in women (e.g., menstruation)

You may be able to prevent migraine attacks or diminish their frequency if you understand what specifically triggers your attacks. Keeping a headache diary may help you identify and monitor the possible migraine triggers you encounter. Once the triggers are identified, you and your doctor can modify your treatment and lifestyle appropriately.

How does MAXALT work during a migraine attack?

Treatment with MAXALT:

1. Reduces swelling of blood vessels surrounding the brain. This swelling results in the headache pain of a migraine attack.
2. Blocks the release of substances from nerve endings that cause more pain and other symptoms of migraine.
3. Interrupts the sending of specific pain signals to your brain.

It is thought that each of these actions contributes to relief of your symptoms by MAXALT.

How should I store MAXALT?

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medication away from heat, light, moisture, and at a controlled room temperature 59°-86°F (15°-30°C). If your medication has expired, throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to do so. Throw away your medicine as instructed. Be sure that the discarded tablets are out of the reach of children.

If you are storing MAXALT-MLT, do not remove the blister from the outer aluminum pouch until you are ready to take the medication inside.

This leaflet provides a summary of information about MAXALT. If you have any questions or concerns about either MAXALT or migraine, talk to your doctor. In addition, talk to your pharmacist or other health care provider.

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

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Issued December 2000

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20-864/S-008 & 20-865/S-009

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	20-864 & 20-865 (005-009)
Sponsor:	Merck
Drug:	rizatriptan (Maxalt)
Proposed Indication:	Migraine
Material Submitted:	CBEs
Correspondence Date:	4/30/01 & 5/4/01
Date Received / Agency:	5/1/01 & 5/8/01
Date Review Completed	5/31/01
Reviewer:	Gerald Tremblay, MD

1. Introduction

Sponsor Merck is submitting supplements to its NDAs for its two marketed forms of rizatriptan, Maxalt Tablets and Maxalt-MLT Orally Disintegrating Tablets. These supplements are Changes Being Effected (CBEs).

CBEs under NDAs 20-864 and 20-865 (Serial nos. 005, 006, 007)

With respect to the 4/30/01 submission, the AE of toxic epidermal necrolysis is proposed to be added to the ADVERSE REACTIONS, *Postmarketing Experience* section. A reformatting of that section is also proposed so that the existing AEs listed there will now have separate headings. The only proposed substantive change, however, will be the addition of TEN. The altered section will now appear as follows:

ADVERSE REACTIONS

...

Postmarketing Experience

...

Cardiovascular: Myocardial ischemia, Myocardial infarction (see WARNINGS)

Cerebrovascular: Stroke

Skin and Skin Appendage: Toxic epidermal necrolysis

Special Senses: Dysgeusia

A second proposed change to the label is under WARNINGS, which currently contains a list of risk factors for CAD. To this list Sponsor proposes adding the risk factor "smoker," based upon postmarketing experience.

CBEs under NDAs 20-864 and 20-865 (Serial nos. 008 & 009)

With respect to the 5/4/2001 submission, there are two proposed labeling changes. The first is a change of address for the company. The second labeling change has to do with hypersensitivity. The proposal is to add a new heading, "General" (under ADVERSE REACTIONS, *Postmarketing Experience*), as follows:

General: *Hypersensitivity*: angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, toxic epidermal necrolysis.

Toxic epidermal necrolysis (TEN) is already present in the current label; this proposal only seeks to move it from a heading "Skin and Skin Appendage" to the "General: *Hypersensitivity*" location. TEN will still be located in the same general place in the label, i.e., under ADVERSE REACTIONS, *Post-Marketing Experience*. The inclusion of angioedema and wheezing are new in the proposed label, and their inclusion reflects post-marketing AE reports.

The Patient Package Insert (PPI) has proposed changes that reflect the foregoing.

In summary, these CBEs are either trivial (addresses and the relocation of an AE (toxic epidermal necrolysis)) or reflect reported AEs.¹

2. Comments

1. The CBEs proposed will strengthen the labeling, and they accurately describe postmarketing experience. They should be approved.

2. In the April 30, 2001, cover letter, Sponsor states, "These supplemental new drug applications [NDA 20-864/S-005 & NDA 20-865/S-006] provide for 1) labeling changes regarding the relationship of menses and migraine attacks, and 2) our completion of a Phase IV commitment in which MRL agreed to conduct ICH pre- and post-natal developmental toxicity studies in rats." (See top of second page of the April 30 cover letter).

I was unable to locate any proposed labeling changes regarding menses and migraine, however. Presumably the pre- and post-natal developmental toxicity data from rats will be submitted when the analysis is done. Sponsor is therefore asked to clarify the quoted statement; if supportive documentation for the statement has been submitted, Sponsor is asked to point it out to us.

¹ This submission (serial numbers 008 & 009) arrived shortly after the ones discussed in the previous section (serial numbers 005, 006, and 007). The proposals of the first section were for some new headings under Postmarketing Experience; the second proposal retained all of the headings except for Skin and Skin Appendage, and moved the skin AE (toxic epidermal necrolysis) under a General: Hypersensitivity heading.

Gerald Tremblay, M.D.
Medical Reviewer, HFD-120

Armando Oliva, MD _____
Team Leader, HFD-120

R. Katz, M.D. _____

cc:
HFD-120
NDA 20-864 & 20-865 (005-009)

Team Leader Note:
I concur with Dr. Tremblay's recommendation.

I point out that the sponsor did submit an efficacy supplement (20-864 S-005, dated 3/10/00) in which they provided new data to support the efficacy of Maxalt in migraine, regardless of the relationship to menses. I reviewed this supplement and it was eventually approved. Therefore, I don't think that we need any additional information from the sponsor regarding comment #2 above.

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/s/

Gerald Tremblay
6/11/01 08:53:38 AM
MEDICAL OFFICER

Armando, there are 2 NDAs affected by these CBEs, so you'll have to sign both of them. jt

Armando Oliva
6/11/01 10:31:23 AM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20-864/S-008 & 20-865/S-009

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

DRUGS: NDA 20-864/Maxalt (rizatriptan benzoate) Tablets
NDA 20-865/Maxalt-MLT (rizatriptan benzoate) Orally Disintegrating Tablets

Supplements: NDA 20-864/S-008 (dated May 4, 2001)
(pending action) NDA 20-865/S-009 (dated May 4, 2001)

Note: The above 2 NDAs share 1 common package insert; therefore, a labeling supplement must be submitted to each NDA when a labeling change is made.

(last approved) From NDA 20-864/S-004, S-005, S-007 (approved on December 11, 2000)
From NDA 20-865/S-005, S-006, S-007 (approved on December 11, 2000)

Label Code: Package Circular #9122108
Patient Product Information Circular #9122202

REVIEW

SLR-008 for NDA 20-864
SLR-009 for NDA 20-865

Dated: May 4, 2001
CBE: Yes
Package Insert #9122109, Patient Package Insert #9122203

These supplements provide for the following revisions:

- A. Package Insert
 1. Company Address - Revised to indicate Worldwide Headquarters location.
 2. ADVERSE REACTIONS, Post-Marketing Experience - Information regarding angioedema and wheezing was added under a new sub- heading "General: Hypersensitivity" and "toxic epidermal necrolysis" was relocated to this section.
- B. Patient Package Insert
 1. What are the possible side effects of MAXALT? - Text has been revised for consistency with the package circular and also revised editorially for clarity.
 2. Company Address - Revised to indicate Worldwide Headquarters location.

Label Comparison Findings:

An electronic comparison of the package insert and patient package insert submitted in NDA 20-864/S-008 (# 9122109 and 9122203) to the approved package insert and patient package insert for Maxalt and Maxalt-MLT (# 9122108 and 9122202) was performed. No changes beyond those provided for in NDA 20-864/S-008 were noted.

STATUS OF REVIEW BY OTHER DISCIPLINES:

1. The clinical review for these applications is complete (see review by Dr. Tremblay dated June 11, 2001). The medical officer recommends approval of these applications and the Neurology Team Leader concurs.

CONCLUSIONS

Recommend approval of supplemental applications, NDA 20-864/S-008 and NDA 20-865/S-009.

Jacqueline H. Ware, Pharm.D.
Regulatory Project Manager

Robbin Nighswander, M.S.
Supervisory Regulatory Health Project Manager

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jackie Ware
4/19/02 03:59:59 PM
CSO

Robbin Nighswander
4/19/02 04:48:52 PM
CSO