20864 / S-004, S-005, S-007

20865 / S-005, S-006, S-007

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Maxalt® Tablets
(Rizatriptan)

NDA 20-864
Supplements: S-004
S-005
S-007

Maxalt MLT®
Orally Disentegrating Tablets
(Rizatriptan)

NDA 20-865
Supplements: S-005
S-006
S-007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-864 S-004, S-005, S-007
NDA 20-865 S-005, S-006, S-007

Merck & Co., Inc.
Attn: Charlene G. Sanders, M.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Sanders:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Maxalt® (rizatriptan) Tablets, and Maxalt MLT® (rizatriptan) Orally Disintegrating Tablets.

NDA 20-864 Maxalt®	NDA 20-865 Maxalt MLT®	Letter Date	Receipt Date
S-004	S-005	November 11, 1999	November 12, 1999
S-005	S-006	March 10, 2000	March 13, 2000
S-007	S-007	November 2, 2000	November 3, 2000

We also refer to your amendments dated April 27, July 5, October 25, 2000 submitted to N20-864/S-005 & N20-865/S-006 and to your amendment dated November 7, 2000, submitted to all of these supplemental applications. Finally, reference is also made to your amendment dated November 29, 2000 submitted to N20-864/S-007 & N20-865/S-007.

NDA 20-864/S-004
NDA 20-865/S-005

These "Changes Being Effected" supplemental new drug applications provide for revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the label, based on post-marketing experience in patients with risk factors predictive of CAD, myocardial ischemia or infarction, cerebrovascular accident, and dysgeusia. Additionally, the Patient Package Insert (PPI) has been updated to reflect the changes to the package insert.

NDA 20-864/S-005
NDA 20-865/S-006

These supplemental new drug applications provide for 1) labeling changes regarding the relationship of menses and migraine attacks, and 2) your response to a Phase IV commitment in which you agreed to conduct ICH pre- and post-natal developmental toxicity study in rats using doses that produce adequate evidence of maternal toxicity.

NDA 20-864/S-007
NDA 20-865/S-007

These "Changes Being Affected" supplemental new drug applications provide for a revision in the ADVERSE REACTIONS:Post-Marketing Experience section of the package insert to add the following reaction: "Skin and Skin Appendage: Toxic Epidermal Necrolysis (TEN)"

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, text for the patient package insert).

Please submit 20 paper 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. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA xx-xxx/S-yyy, S-zzz." Approval of these submissions by FDA is not required before the labeling is used.

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

Phase IV Commitment:

We also note that your supplemental applications dated March 10, 2000 (NDA 20-864 S-005; NDA 20-865 S-006), provide results from your post marketing commitment to "do an ICH pre- and post-natal developmental toxicity study in rats using doses that produce adequate evidence of maternal toxicity."

We have completed the review of your post marketing data and conclude that the above commitment has been fulfilled.

This completes all of your post marketing commitments for this application.

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 Robbin Nighswander, R.Ph., Regulatory Management Officer, at (301) 594-5531.

Sincerely,

/S/

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

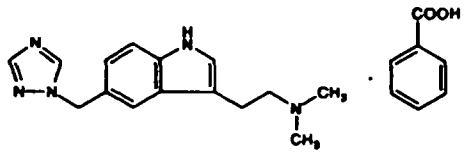
Attachment

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

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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 $5\text{-}HT_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the $5\text{-}HT_{1B/1D}$ 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 $5\text{-}HT_{1B/1D}$ 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

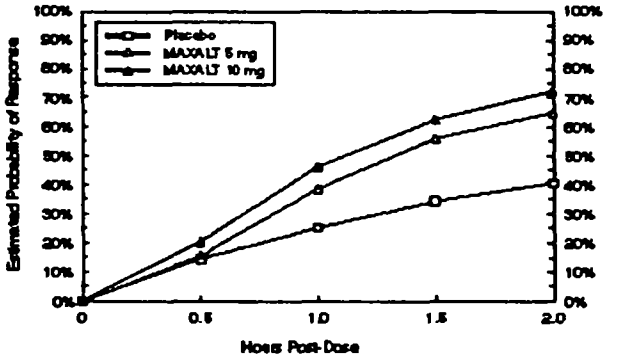
Study	Placebo	MAXALT Tablets 5 mg	MAXALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* 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††

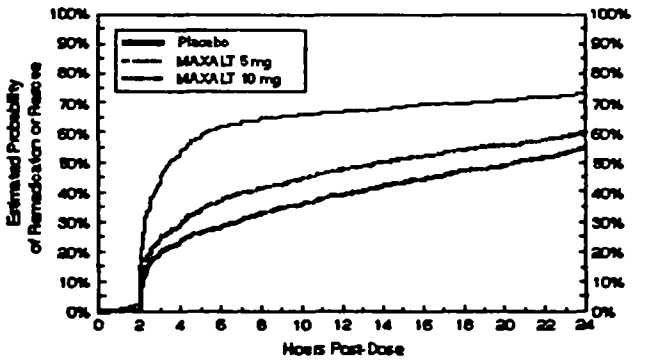


†† Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 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. 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.

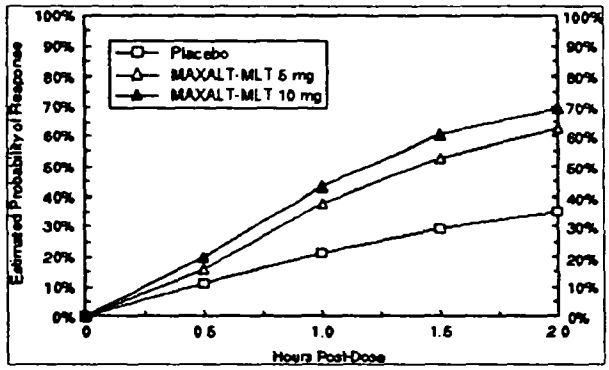
Table 2
Response Rates 2 Hours Following Treatment of Initial Headache

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‡

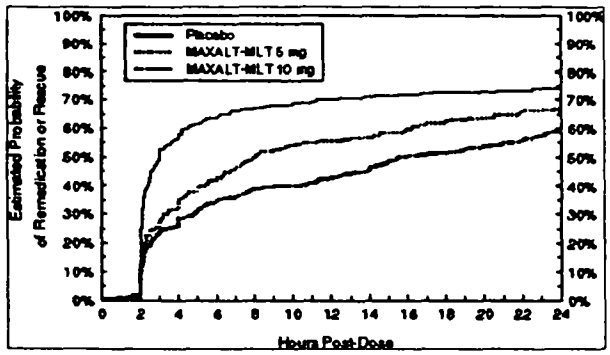


‡ Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT-MLT or placebo. The averages displayed are based on pooled data from 2 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1 and 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-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, 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-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. 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-HT$_1$ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 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 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-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 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

	% 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.

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.

Skin and Skin Appendage: Toxic epidermal necrolysis.

Special Senses: Dysgeusia.

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.

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

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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-HT_1 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
- about all drugs you are taking or plan to take, including those obtained without a prescription, and those you normally take for a migraine.

*** The brands listed are the trademarks of their respective owners and are not trademarks of Merck & Co., Inc.

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 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.

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, tongue swelling, changes in appetite, burping and inability of the tongue to move.

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Skin - Flushing (redness of the face lasting a short time), hot flashes, sweating, itching, rash, hives, 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, hiccups and swelling of the throat.

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

Miscellaneous - Chills, heat sensitivity, swelling, bloating, hangover effect, fever, fainting, dizziness on standing up, warm/cold sensations, dehydration and changes in urination and menstruation.

In addition, bad taste has occurred.

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 (such as a rash or itching) 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.

Issued ~~August 1999~~

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

USER FEE DUE-DATE: January 13, 2001

Maxalt® Tablets
&
Maxalt MLT®
Orally Disentegrating Tablets

(Rizatriptan)

NDA 20-864/S-004, S-005, & S-007
NDA 20-865/S-005, S-006, & S-007

Classification: S

Date:	Document:	Supp:	Tab:
June 23, 2000	Medical Review: A. Oliva, M.D.	S-004/5	A
July 10, 2000	Pharmacology Review: S. Stolzenberg, Ph.D.	S-005/6	B
July 11, 2000	Medical Review: A. Oliva, M.D.	S-005/6	C
October 10, 2000	FAX to firm: Re: FDA proposed labeling	S-004/5 & S-005/6	D
November 22, 2000	Medical Review: A. Oliva, M.D.	S-007/7	E
November 30, 2000	Statistical Review: Yuan-Li Shen, Dr. PH	S-005/6	F
December 4, 2000	Medical Review (DRAFT): A. Oliva, M.D.	S-007/7	G
December 4, 2000	Labeling Review: R. Nighswander, M.S.	All Supps	H

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-864**
Sponsor:	**Merck**
Drug:	**Maxalt**
Proposed Indication:	**migraine**
Material Submitted:	**Labeling Changes Being Effected**
Correspondence Date:	**11/11/99**
Date Received / Agency:	**11/11/99**
Date Review Completed	**6/23/00**
Reviewer:	**Armando Oliva, MD**

1. Introduction

This submission contains labeling changes being effected which are designed to strengthen the currently approved product labeling. These are based on post-marketing reports.

2. Labeling History

The original Maxalt labeling was approved at the time of NDA approval on 6/29/98. Changes being effected submitted on 1/8/99 (S-001) and in the annual report (9/9/99) included a pregnancy registry, minor editorial changes to the adverse events section, dropping of the 500 unit bottle, and addition of the site of the manufacturing of tablet and MLT were added. These changes were approved at the end of 11/99, along with the approval of an efficacy supplement which included results of a new efficacy study with the MLT formulation. This labeling included revised Kaplan-Meier curves for the MLT.

Just approved on 6/21/00 were labeling changes as part of an efficacy supplement (SE5-002) containing PK and efficacy data in adolescents.

3. Sponsor Proposed Labeling Changes

The sponsor proposes changes to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections, as well as changes to the patient product information (PPI).

WARNINGS

The warnings section has been revised based on post-marketing experience. The words "other" have been removed from cardiac and cerebrovascular events sections, as shown below.

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).

PRECAUTIONS
The title of the subsection "Use in the Elderly" has been revised to "Geriatric Use" for compliance with the Geriatric Final Rule (21 CFR 201.57(f)(10)).

ADVERSE REACTIONS
A post-marketing experience subsection has been created and the following information has been added based on postmarketing reports.

Post-Marketing Experience

The following adverse reaction has also been reported:
Special Senses: Dysgeusia.

Patient Product Information
What should I tell my doctor before and during treatment with MAXALT?
The term "stroke" and "blood vessel disease" have been added for consistency with the revised side effects section.

About any risk factors for heard disease or blood vessel disease
- High blood pressure or diabetes (etc.)
- Family history of heart disease or blood vessel disease

What are the possible side effects of MAXALT?
This section has been revised for consistency with the package circular.

In addition, bad taste has occurred.

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?)

4. Discussion

As post-marketing experience grew, rare reports of these same events were submitted for the new drugs in question. Both and now Merck, are appropriately changing their labeling to include their drug as one that also has these serious post-marketing adverse reports. The question is whether the changes are strong enough. In the case of I felt that the changes should have been a bit stronger, and recommended specific wording for them to adopt. I recommend the same wording below.

I note that the sponsor has not provided details of the cases that resulted in the proposed changes. However, given the fact that rizatriptan is a member of a class which is known to cause serious cardiac events (and has appropriate warnings to this effect), it is not surprising that such reports have emerged. It seems appropriate to adopt the "class-labeling" for postmarketing adverse events that currently exists for sumatriptan and zolmitriptan.

5. Reviewer Proposed Labeling Changes

My proposed changes are outlined below. They are similar to the recommendations I made for labeling last fall. The sponsor's recommendations for the Warnings: cerebrovascular events section and the PPI are accepted without changes.

> WARNINGS
> **Cardiac Events and Fatalities Associated with 5-HT_1 Agonists:** Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of rizatriptan. 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. 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 10mg.
>
> *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-HT_1 agonists. Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 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).

ADVERSE REACTIONS
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.
Cerebrovascular: stroke.
Special Senses: dysgeusia.

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

About any risk factors for heard disease or blood vessel disease

- High blood pressure or diabetes (etc.)
- Family history of heart disease or blood vessel disease

What are the possible side effects of MAXALT?

In addition, bad taste has occurred.

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?)

6. Comments

The proposed labeling changes described above are similar to the changes I recommended for [redacted] in response to a similar submission. I recommend they be incorporated into the current product labeling, the most recent version of which was just approved on 6/21/00.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. /S/

ao 6/23/00
cc:
HFD-120
NDA 20-864
electronic copy-Katz

NDAs 20-864 and 20-865

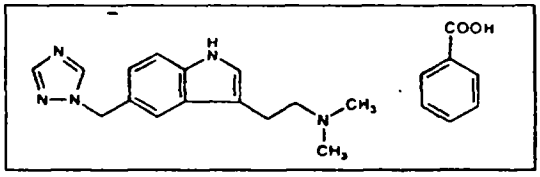
REVIEW AND EVALUATION OF TOXICOLOGY DATA
Phase 4 Commitment

Sidney J. Stolzenberg
July 10, 2000

NDA AMENDMENT: #5, DATED: 3/10/00
CENTER RECEIPT DATE: 3/13/00
REVIEWER RECEIPT DATE: 4/12/00

SPONSOR: Merck & Co, Inc.
West Point, Pa
Phone: 610-397-7597 (Dennis M Erb)

DRUG: MAXALT™ (rizatriptan benzoate) and MAXALT-MLT™



MW: 269.4 (free base)

FORMULATION: 5 and 10 mg (as base) for oral administration as tablets (NDA 20-864) and as orally disintegrating tablets (NDA 20-865).

PHARMACOLOGICAL CLASS: Serotonin receptor subtype 5-$HT_{1B/1D}$ partial agonist

PROPOSED INDICATION: Acute treatment of migraine attacks

DOSAGE REGIMEN: One tablet

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A. BACKGROUND

The Maxalt NDAs were approved by the Agency on June 29, 1998. Doses selected for the prenatal-postnatal development study in rats were considered too low by the reviewing pharmacologist, Dr. Thomas Steele, because maternal toxicity was not evident at the highest dose selected (100 mg/kg/day). The pharm-tox team, which included Drs. Thomas Steele, Glenna Fitzgerald and Ed Fisher, examined the proposed protocol for a Phase 4 commitment (doses of 5, 100 and 250 mg/kg/day) and found the design of the study acceptable for satisfying the Phase 4 commitment. (See e-mail message from T. Steele to L. Chen, dated 9/22/98, in Appendix).

B. REVIEW OF TOXICOLOGY REPORT

Oral Gavage Pre- and Post-natal Development Study in the Rat

Study No. TT #98-742-0

Performing Laboratory: Merck Research Laboratories
West Point, Pa

Dates Study Performed: Study initiated 11/15/98, necropsies completed 4/7/99

Quality Assurance: A statement of GLP compliance is included.

Test Substance: Lot no. L-705,126-004B024; ——

Test Animals: Female Sprague-Dawley Crl:CD(SD)IGS BR rats, (Charles River, Raleigh, NC), approximately 10 weeks old, weighing 209-262 g at the time of mating,

Doses Administered: 0, 5, 100 and 250 mg/kg/day (dosage based on free base)

Procedure: Rizatriptan was administered daily in deionized water to 22 F_0 females/group between gestation day (GD) 6 and postpartum day (PPD) 20. Controls received vehicle and the dosing volume for all 4 groups was 10 mL/kg, based on most recent body weights. All animals on test were examined daily for clinical signs and mortality. Body weights of F_0 dams were recorded on 10 or 11 time periods during gestation and on PPD 0, 3, 7, 10, 14, 17 and 21; food consumption was measured at 2 day intervals at 5 time periods during gestation and at 4 day intervals during lactation; PPD 1 to 5 and PPD 8 to 12. Each female was observed at 4 time periods between 7:30 a.m. and 3 p.m. each weekday and at 2 time periods on weekends to determine if delivery had occurred and for possible difficulties in parturition. When delivery had occurred by 7:30 a.m., an additional whole day was assigned to gestation period. When delivery occurred between 7:30 a.m. and 3 p.m., an additional half day was assigned. The F_0 females were sacrificed on PPD 21 to 24 and the uterus of each was examined to count metrial glands and to determine pregnancy status if delivery had not occurred. At necropsy, gross examinations of abdominal and thoracic viscera were performed.

F_1 rats were observed daily for physical signs and mortality and body weights were recorded PPD 0, 7, 14 and 21. On PPD 0, 10 pups per litter (5 of each sex where possible) were randomly selected and identified by tattoo. On PPD 3, each litter was reduced to 4 per sex, and to maintain litter size of 8 per sex on PPD 3, fostering within groups was performed when necessary. On PPD 21, two per sex per litter were selected for postweaning evaluation. The non-selected pups were killed and discarded without further examination. Pups found dead were fixed in 10% neutral formalin for possible examination but further examinations were not required. All pups were examined for external malformations at birth and subsequently throughout lactation.

Starting on PPD 24, F_1 rats were weighed weekly until breeding or termination. They were inspected daily for physical signs and mortality. Developmental parameters measured included vaginal opening starting on PPD 28 and preputial separation was assessed starting on PPD 38. Behavioral assessment on 1 male and 1 female per litter included passive avoidance tests (on both PPD 35$\pm$1and 41$\pm$1), auditory startle (on PPD 63$\pm$2), open field motor activity (on PPD 70$\pm$2) and ophthalmologic exams were performed on all control and high dose rats (on PPD 49$\pm$2).

Mating (1 male and 1 female/litter; not siblings) during week 8 was assessed for up to 20 nights of cohabitation. F_1 mated females were examined daily for mortality and twice daily for physical signs until sacrifice. Body weights were recorded weekly, but females that mated were weighed on GD 0, 7, 14, 20, 24 and on PPD 0. Length of gestation was determined. Animals not used for mating were killed in postweaning Week 12, and F_1 dams were killed within a week after delivery without further examination. Mated females that did not deliver and non-mated females were killed on PPD 24.

Result; F_0 Dams: (limited to mortality and compound related effects)

Mortality: No deaths, but 1 dam at mid dose with no live pups was killed on PPD 1.

Physical Signs: Salivation was occasionally noted in 5 females at high dose, considered to related to poor palatability of the drug at that concentration.

Body Weight and Body Weight Gain: Sponsor calculated that in the mid and high dose groups, there were treatment-related decreases in mean maternal body weight gains between GD 6 and 21 (6.7 and 16.7%, respectively), and treatment-related effects on normal pattern of body weight gains during lactation in mid and high dose groups. These effects on weight gain are not biologically meaningful because 1) none of them were statistically significant, 2) the effects were small but when based on percent decrease in body weight gain, the numbers become exaggerated and 3) if there was an differences in patterns of weight gain between control and treated groups during lactation, as suggested by the sponsor, they were, at most, transient in nature and were no longer present by PPD 21. (See Tables 1 and 2 on pages 4 and 5). Sponsor also claimed that there were decreases in food intake at mid and high doses, but these effects were also small and not statistically significant (See sponsor's Table 3 on page 5).

BLE 1. RIZATRIPTAN BENZOATE ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE MATERNAL BODY WEIGHTS (GRAMS ±S.D.) OF F0 FEMALES

TREATMENT GROUP	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DAY
GESTATIONAL PERIOD				
DAY 0	229 ± 9(22)	231 ± 12(22)	233 ± 14(21)	235 ± 10(22)
DAY 6	265 ± 13	266 ± 16	271 ± 18	271 ± 12
DAY 8	275 ± 14	274 ± 17	274 ± 18	267 ± 14
DAY 10	284 ± 14	284 ± 17	282 ± 20	272 ± 14
DAY 12	295 ± 16	296 ± 20	292 ± 19	281 ± 16
DAY 14	305 ± 16	307 ± 20	302 ± 20	291 ± 17
DAY 16	321 ± 19	327 ± 23	320 ± 20	309 ± 19
DAY 18	345 ± 18	351 ± 23	343 ± 23	330 ± 16
DAY 20	374 ± 21	380 ± 27	369 ± 26	356 ± 17
DAY 21	385 ± 23	393 ± 27	383 ± 27	370 ± 18
DAY 22	389 ± 16(08)	402 ± 21(07)	412 ± 25(09)	381 ± 12(05)

(N) = GROUP SIZE AND APPEARS ONLY IF DIFFERENT FROM PREVIOUS N. SEE INDIVIDUAL TABLE FOR EXCLUSIONS.

LE 1. RIZATRIPTAN BENZOATE ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE MATERNAL BODY WEIGHTS (GRAMS ±S.D.) OF F0 FEMALES

TREATMENT GROUP:	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DAY
LACTATIONAL PERIOD				
DAY 0	262 ± 19(22)	288 ± 16(22)	283 ± 25(21)	275 ± 19(22)
DAY 3	299 ± 19	305 ± 20	297 ± 22(20)	281 ± 14
DAY 7	314 ± 19	315 ± 23	306 ± 25	293 ± 13
DAY 10	323 ± 23	326 ± 20	316 ± 24	299 ± 16
DAY 14	332 ± 23	336 ± 19	327 ± 27	309 ± 15
DAY 17	327 ± 23	338 ± 16	328 ± 26	310 ± 15
DAY 21	311 ± 19	318 ± 20	319 ± 25	304 ± 14

(N) = GROUP SIZE AND APPEARS ONLY IF DIFFERENT FROM PREVIOUS N. SEE INDIVIDUAL TABLE FOR EXCLUSIONS.

LE 2. RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION TT #98-742-
AVERAGE MATERNAL BODY WEIGHT CHANGES (GRAMS ±S.D.) OF F0 FEMALES

MENT GROUP:	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DAY
GESTATIONAL PERIOD				
DAY 0 TO 6	36 ± 7(22)	35 ± 7(22)	35 ± 8(21)	36 ± 7(22)
DAY 6 TO 21	120 ± 14	128 ± 17	112 ± 16	100 ± 11
DAY 0 TO 21	156 ± 16	163 ± 21	150 ± 18	136 ± 13
LACTATIONAL PERIOD				
DAY 0 TO 7	32 ± 12(22)	27 ± 15(22)	22 ± 13(20)	18 ± 12(22)
DAY 7 TO 14	18 ± 10	21 ± 12	21 ± 11	15 ± 7
DAY 14 TO 21	-22 ± 11	-18 ± 10	-8 ± 11	-5 ± 7
DAY 0 TO 21	28 ± 12	30 ± 13	35 ± 18	29 ± 14

(N) = GROUP SIZE AND APPEARS ONLY IF DIFFERENT FROM PREVIOUS N. SEE INDIVIDUAL TABLE FOR EXCLUSIONS

LE 3. RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE MATERNAL FOOD CONSUMPTION (GRAMS/DAY ±S.D.) OF F0 FEMALES

MENT GROUP:	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DAY
GESTATIONAL PERIOD (A)				
DAY 5	25 ± 2(22)	26 ± 3(22)	26 ± 2(21)	25 ± 2(22)
DAY 8	26 ± 2	26 ± 4	23 ± 3	20 ± 4
DAY 12	27 ± 2	28 ± 3	25 ± 3	22 ± 4
DAY 16	27 ± 2	28 ± 3	26 ± 3	25 ± 3
DAY 20	26 ± 3	27 ± 4	25 ± 3	25 ± 3
LACTATIONAL PERIOD (B)				
DAY 5	39 ± 5(22)	40 ± 7(21)	37 ± 9(19)	32 ± 3(21)
DAY 12	58 ± 5	59 ± 5(22)	54 ± 5(20)	50 ± 4(22)

(A) = INDICATED DAY DENOTES END OF 2-DAY INTERVAL.

(B) = INDICATED DAY DENOTES END OF 4-DAY INTERVAL.

(N) = GROUP SIZE AND APPEARS ONLY IF DIFFERENT FROM PREVIOUS N. SEE INDIVIDUAL TABLE FOR EXCLUSIONS

Pregnancy, Parturition and Gestation Length: No effects were noted (See Table 4 on page 7).

Result; F_1 Pups: (limited to compound related effects)

Mortality: As noted by the investigators, there were treatment-related increases in dead pups per litter at birth for mid (5.72% and high (4.17%) doses, compared to controls (0%). There were also increases in litter mean incidences of deaths during PPD 1 to 3 at mid (6.4%) and high (4.1%) doses compared to controls (0.9%). (See Sponsor's Table 5 on page 7).

Body Weight: During lactation, there were treatment-related decreases in mean pup weights (both male and female) at mid and high doses, compared to controls. (See Sponsor's Table 5 on page 7). The decrease in mean body weight in females at high dose, compared to control, persisted at high dose into adulthood to post-weaning Weeks 8 and 12 ($P<05$ by the trend test; see Table 7 and 8 on page 8 and 9). In males, decreases in mean body weight compared to control were evident at both mid and high doses, which also persisted into adulthood to post-weaning Week 8 ($P<05$ by the trend test; see Table 9 on page 10).

Developmental and Behavioral Assessment: There were no treatment-related effects on sexual maturity (vaginal canalization or preputial separation). There were significant treatment-related increases in number of trials to criterion in the first passive avoidance test conducted on PPD 35$\pm$1 for females in the 250 mg/kg/day and for males in the 100 and 250 mg/kg/day treated groups (See sponsor's Table 13 on page 11). The effect was not evident in the second passive avoidance test conducted on PPD 42$\pm$1.

TABLE 4. RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION TT #98-742-0
SUMMARY OF REPRODUCTIVE PERFORMANCE OF F0 FEMALES

	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG DAY
FEMALES	22	22	22	22
PREGNANT FEMALES	22	22	21	22
DIED DURING GESTATION	0	0	0	0
SACRIFICED DURING GESTATION	0	0	0	0
DIED OR SACRIFICED DURING PARTURITION	0	0	0	0
DIED OR SACRIFICED POSTPARTUM	0	0	1	0
FEMALES WITH LIVE PUPS PND 0 (A)	22	22	21	22
FEMALES WITH NO LIVE PUPS PND 0 (A)	0	0	0	0
FEMALES WITH LIVE PUPS PND 21	22	22	20	22
NONPREGNANT FEMALES	0	0	1	0
LIVE	0	0	1	0
DIED	0	0	0	0
SACRIFICED	0	0	0	0
NOT BRED	0	0	0	0
FEMALES WITH LIVE PUPS/PREGNANT FEMALES, % (A)	100	100	100	100
LENGTH OF GESTATION (DAYS) (A)	22.3 ± 0.4	22.2 ± 0.4	22.2 ± 0.3	22.1 ± 0.4

A = INCLUDES ONLY FEMALES COMPLETING DELIVERY

BLE 5. RIZATRIPTAN BENZOATE. ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION TT #98-742-0
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING

	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DAY
ENTAL FEMALES	22	22	21	22
LANTS PER FEMALE ±S.D.	15.4± 1.7	15.1± 2.3	14.8± 1.9	14.7± 1.5
OSTIMPLANTATION SURVIVAL				
DAY 0 (L.M.) ±S.D.	93.4± 6.0	94.0± 9.2	90.7±19.6	92.8± 8.3
WITH LIVE PUPS DAY 0 POSTPARTUM	22	22	21	22
WITH LIVE PUPS DAY 21 POSTPARTUM	22	22	20	22
AL PUPS DELIVERED				
LIVE PUPS (SEX RATIO, L.M.)	316(0.49)	311(0.51)	284(0.43)	300(0.50)
DEAD PUPS (%, L.M.±S.D.)	0(0.00± 0.00)	5(1.72± 6.75)	13(5.72±19.65)	13(4.17± 5.10)
IVE PUPS DELIVERED (L.M.) ±S.D.	100.0± 0.0	98.3± 6.7	94.3±19.6	95.8± 5.1
E PUPS PER LITTER ±S.D.				
OSTNATAL DAY 0	14.4± 1.9	14.1± 2.4	13.5± 3.3	13.6± 1.7
OSTNATAL DAY 3	8.0± 0.0	8.0± 0.0	8.0± 0.0	8.0± 0.0
OSTNATAL DAY 7	8.0± 0.0	8.0± 0.2	8.0± 0.0	7.9± 0.3
OSTNATAL DAY 14	8.0± 0.2	8.0± 0.2	8.0± 0.2	7.9± 0.3
OSTNATAL DAY 21	7.9± 0.4	8.0± 0.2	8.0± 0.2	7.9± 0.3
DEATHS (% PUP DEATHS ±S.D.) (L.M.)				
POSTNATAL DAYS 1 - 3	3(0.9± 2.3)	4(1.4± 3.0)	6(6.4±21.7)	13(4.1± 7.2)
POSTNATAL DAYS 4 - 7	0(0.0± 0.0)	1(0.6± 2.7)	0(0.0± 0.0)	2(1.1± 3.7)
POSTNATAL DAYS 8 - 14	1(0.6± 2.7)	0(0.0± 0.0)	1(0.6± 2.8)	0(0.0± 0.0)
POSTNATAL DAYS 15 - 21	1(0.6± 2.7)	0(0.0± 0.0)	0(0.0± 0.0)	0(0.0± 0.0)
POSTNATAL DAYS 4 - 21	2(1.1± 5.3)	1(0.6± 2.7)	1(0.6± 2.8)	2(1.1± 3.7)
E FEMALE PUP WEIGHT (GM) (L.M.) ±S.D.				
POSTNATAL DAY 0	6.0 ± 0.4	6.0 ± 0.3	5.8 ± 0.4	5.4 ± 0.4
POSTNATAL DAY 7	15.9 ± 1.3	16.0 ± 1.5	14.1 ± 1.2	12.9 ± 1.1
POSTNATAL DAY 14	32.5 ± 2.4	33.0 ± 2.7	29.2 ± 2.7	26.2 ± 2.2
POSTNATAL DAY 21	53.6 ± 4.0	54.7 ± 3.5	49.1 ± 4.9	44.2 ± 4.2
E MALE PUP WEIGHT (GM) (L.M.) ±S.D.				
POSTNATAL DAY 0	6.5 ± 0.5	6.4 ± 0.4	6.1 ± 0.4	5.8 ± 0.4
POSTNATAL DAY 7	16.8 ± 1.3	16.4 ± 1.6	14.6 ± 1.4	13.7 ± 1.3
POSTNATAL DAY 14	34.0 ± 2.4	33.8 ± 3.0	30.2 ± 3.1	27.6 ± 2.6
POSTNATAL DAY 21	56.6 ± 4.1	56.5 ± 4.4	51.5 ± 6.1	47.3 ± 4.7

CENT POSTIMPLANTATION SURVIVAL TO DAY 0 = (NO. LIVE PUPS DELIVERED/TOTAL NO. METRIAL GLANDS) X 100.
M = LITTER MEAN
O = (TOTAL NO. LIVE FEMALE PUPS/TOTAL NO LIVE PUPS)
CLUDES PUPS FOR WHICH SEX COULD NOT BE DETERMINED

RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE BODY WEIGHTS (GRAMS ±S.D.) OF F1 FEMALES PRIOR TO COHABITATION

ATMENT UP	POSTWEANING WEEK (PW) 1	2	3	4	5	6
ROL						
MEAN F	76 ± 11(44)	116 ± 19	155 ± 23	190 ± 19(43)	211 ± 21	233 ± 24
/KG/DAY						
MEAN F	79 ± 7(44)	122 ± 12	163 ± 11	195 ± 13	221 ± 16	244 ± 17
MG/KG/DAY						
MEAN F	73 ± 8(40)	115 ± 12	153 ± 14	185 ± 17	209 ± 19	232 ± 23
MG/KG/DAY						
MEAN F	68 ± 6(41)	107 ± 11	146 ± 13	177 ± 14	199 ± 17	221 ± 20

) = NUMBER OF ANIMALS IS INDICATED IN THE PARENTHESIS AND APPLIES TO THE FOLLOWING PWW.

ED

RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE BODY WEIGHTS (GRAMS ±S.D.) OF F1 FEMALES PRIOR TO COHABITATION

REATMENT ROUP	POSTWEANING WEEK (PW) 7	8	WT CHANGE (PW 1-8)	STATISTICAL RESULTS[a]
NTROL				
MEAN F	246 ± 28(43)	261 ± 29	184 ± 27	
MG/KG/DAY				
MEAN F	255 ± 20(44)	274 ± 22	195 ± 22	
0 MG/KG/DAY				
MEAN F	246 ± 25(40)	262 ± 26	189 ± 23	NS
0 MG/KG/DAY				
MEAN F	234 ± 21(41)	249 ± 22	180 ± 19	S

(N) = NUMBER OF ANIMALS IS INDICATED IN THE PARENTHESIS AND APPLIES TO THE FOLLOWING PWW.

S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.

NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.

- BODY WEIGHT CHANGES BETWEEN POSTWEANING WEEKS 1 AND 8 WERE ANALYZED FOR LINEAR AND AVERAGE TIME RESPONSES.

TABLE 8. RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE BODY WEIGHTS (GRAMS ±S.D.) OF F1 FEMALES

TREATMENT GROUP	POSTWEANING WEEK (PWW) 9	10	11	12	WT CHANGE (PWW 9-12)	STATISTICAL RESULTS[a]
CONTROL						
MEAN F	273 ± 30(22)	285 ± 35	294 ± 35	300 ± 35	27 ± 10	
5 MG/KG/DAY						
MEAN F	288 ± 20(22)	301 ± 20	308 ± 23	314 ± 24	26 ± 9	
100 MG/KG/DAY						
MEAN F	270 ± 28(20)	284 ± 29	298 ± 41(21)	304 ± 43	28 ± 11	NS
250 MG/KG/DAY						
MEAN F	260 ± 26(20)	269 ± 30	279 ± 32(21)	287 ± 33	25 ± 9	S

(N) = NUMBER OF ANIMALS IS INDICATED IN THE PARENTHESIS AND APPLIES TO THE FOLLOWING PWW.

S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.

NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.

a = BODY WEIGHT CHANGES BETWEEN POSTWEANING WEEKS 9 AND 12 WERE ANALYZED FOR LINEAR AND AVERAGE TIME RESPONSES

RIZATRIPTAN BENZOATE ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION TT #98-742-0
AVERAGE BODY WEIGHTS (GRAMS ±S.D.) OF F1 MALES PRIOR TO COHABITATION

ATMENT UP	POSTWEANING WEEK (PWW) 1	2	3	4	5	6
ROL						
MEAN M	83 ± 9(44)	136 ± 13	201 ± 17	266 ± 22	326 ± 26	372 ± 3
/KG/DAY						
MEAN M	85 ± 9(44)	141 ± 14	208 ± 18	273 ± 22	335 ± 26	382 ± 2
MG/KG/DAY						
MEAN M	78 ± 9(40)	130 ± 14	193 ± 20	256 ± 25	316 ± 30	363 ± 3
MG/KG/DAY						
MEAN M	74 ± 6(44)	124 ± 10	186 ± 14	247 ± 18	304 ± 21	349 ± 2

) = NUMBER OF ANIMALS IS INDICATED IN THE PARENTHESIS AND APPLIES TO THE FOLLOWING PWW

NTINUED
9 RIZATRIPTAN BENZOATE ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
AVERAGE BODY WEIGHTS (GRAMS ±S.D.) OF F1 MALES PRIOR TO COHABITATION

REATMENT GROUP	POSTWEANING WEEK (PWW) 7	8	WT CHANGE (PWW 1-8)	STATISTICAL RESULTS?
NTROL				
MEAN M	421 ± 36(44)	458 ± 40	375 ± 36	
MG/KG/DAY				
MEAN M	430 ± 32(44)	469 ± 35	384 ± 32	NS
0 MG/KG/DAY				
MEAN M	408 ± 39(40)	444 ± 43	366 ± 36	S
0 MG/KG/DAY				
MEAN M	394 ± 28(44)	429 ± 33	355 ± 31	S

(N) = NUMBER OF ANIMALS IS INDICATED IN THE PARENTHESIS AND APPLIES TO THE FOLLOWING PWW.

S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.

NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.

a = BODY WEIGHT CHANGES BETWEEN POSTWEANING WEEKS 1 AND 8 WERE ANALYZED FOR LINEAR AND AVERAGE TIME RESPONSES.

TABLE 13. RIZATRIPTAN BENZOATE: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION TT #98-742-0
SUMMARY OF PASSIVE AVOIDANCE TESTING OF F1 GENERATION

	FEMALES			
	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG DAY
DAYS 34 TO 36 POSTNATAL - SESSION 1				
NO. ANIMALS TESTED	21[a]	22	19[a]	20
MEAN TRIALS TO CRITERION ± S.D.	7.0 ± 2.7	6.3 ± 2.2	7.0 ± 2.1[NS]	7.5 ± 3.3[S]
NO. NOT ACHIEVING CRITERION	1	0	3	4
DAYS 41 TO 43 POSTNATAL - SESSION 2				
NO. ANIMALS TESTED	20[a]	22	16[a]	16
MEAN TRIALS TO CRITERION ± S.D.	4.2 ± 1.4	4.2 ± 1.5	4.2 ± 0.9	5.2 ± 2.0[NS]
NO. NOT ACHIEVING CRITERION	0	0	0	0

S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE

NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.

a = SEE INDIVIDUAL TABLE FOR EXCLUSIONS

'INUED
LE 13. RIZATRIPTAN BENZOATE. ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS WITH POSTWEANING EVALUATION. TT #98-742-0
SUMMARY OF PASSIVE AVOIDANCE TESTING OF F1 GENERATION

	MALES			
	CONTROL	5 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG DAY
; 34 TO 36 POSTNATAL - SESSION 1				
). ANIMALS TESTED	22	22	20	22
:AN TRIALS TO CRITERION ± S.D.	5.5 ± 1.4	5.5 ± 1.1[NS]	6.3 ± 1.6[S]	7.0 ± 3.3[S]
). NOT ACHIEVING CRITERION	0	0	1	2
; 41 TO 43 POSTNATAL - SESSION 2				
). ANIMALS TESTED	22	22	19	20
:AN TRIALS TO CRITERION ± S.D.	4.0 ± 1.1	3.7 ± 0.6	3.8 ± 0.6	4.2 ± 0.8[NS]
). NOT ACHIEVING CRITERION	0	0	0	0

= TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.

. = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.

C. SUMMARY AND EVALUATION

In the current study, virtually no toxicity to the F_0 dams were noted at all 3 doses tested. Sponsor claimed that females in the 100 and 250 mg/kg/day treated groups gained less weight between gestation days 6 and 21, and between postpartum days 0 and 7, with concomitant decreases in food intake. The effects on weight gain noted by the sponsor appear to be exaggerated because they are based on percent decrease in body weight compared to controls. The decreases in body weight gain were small in proportion to their mean body weights, they were not statistically significant and were, at most, transient in nature. The decreases in food intake were also small and not statistically significant.

There were, however, small decreases in mean body weight of male and female F_1 pups at birth and throughout the period of lactation in the 100 and 250 mg/kg/day treated groups compared to controls. The decreases in mean body weight persisted into adulthood to post-weaning Weeks 8 and 12 in females and to termination (post-weaning Week 8) in males. These differences were statistically significant by the trend test ($P<0.05$) at 250 mg/kg/day in females and at 100 and 250 mg/kg/day in males.

Impaired performance of the F_1 pups was noted in the first session of a passive avoidance test conducted on PPD 35 ± 1 for females at 250 mg/kg/day and for males at 100 and 250 mg/kg/day. This effect suggests a decrease in learning capacity, a functional deficit observed 5 weeks postpartum and 2 weeks after discontinuation of treatment, with males being more affected than females. The effect was not evident in the second passive avoidance test conducted on PPD 42 ± 1, which suggests that after achieving criterion in the first session (learning), there was no effect on memory retention.

It should also be noted that although there was no effect on mortality in the F_0 dams, there were small compound related increases in dead pups/litter for mid and high dose groups in F_1 pups at birth and during the first 3 days of lactation. Nevertheless, there was virtually no effect on number of live pups/litter in any of these groups.

Sponsor concluded that the no-effect level for both the F_0 dams and F_1 pups was 5 mg/kg/day. However, we conclude that the no-effect level was $\geq$250 mg/kg/day for the dams because the decreases in weight gain noted for the pregnant and lactating females were negligible, not statistically significant, and at most and transient in nature. However, we agree that the no-effect level for the F_1 pups was 5 mg/kg/day, based on mortality at birth and during the first 3 days postpartum, decreased body weight at birth and during lactation which persisted into adulthood, and delay in passive avoidance on PPD 35 ± 1.

It is concluded that this drug was shown to have effects on developmental toxicity in rats at doses that are substantially below maternal toxicicity.

D. RECOMMENDATIONS

A. Sponsor has satisfied the Phase 4 requirement for these NDAs. The design of the pre- and post-natal developmental study in rats and the doses selected were considered acceptable for the Phase 4 commitment. (See e-mail message from T. Steele to L. Chen, dated 9/22/98, in Appendix A). The study is considered to be acceptable.

B. The final printed labeling for the drugs formulations has been approved (See the Division letter to Merck and Co., Inc, dated 6/21/00 in Appendix B). Under *Pregnancy: Pregnancy Category C*, sponsor is recommending modifications based on the outcome of the presently submitted study. The following shows all the proposed editorial revisions followed by their rationale for the proposed changes.

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 effec~~ [illegible] ~~occurred in the absence of any apparent maternal toxicity in this study.~~

[illegible] The developmental no-effect dose was 2 mg/kg/day (maternal exposure approximately ~~1.5~~ [illegible] 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.~~

The following is our recommendation for the proposed revised labeling of the first paragraph of the Pregnancy section.

Pregnancy: Pregnancy Category C
In a general reproductive toxicity 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 exposures 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 a 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 any apparent maternal toxicity.

Reasons: Most of the wording in the above paragraph is the same or similar to that proposed by the sponsor. Some changes were made which we consider to be appropriate. The company proposed removal of the following sentence, which is very similar to the final printed labeling (FLP) that had been previously approved by the Division.

All of these effects on the offspring in both developmental toxicity studies occurred in the absence any apparent maternal toxicity.

Sponsor concluded that the no-effect level for both the F_0 dams (based solely on decreased body weight gain) and F_1 pups was 5 mg/kg/day in the pre-and post-natal developmental toxicity study. We conclude that the no-effect level was $\geq$250 mg/kg/day for the dams because the decreases in body weight gain noted in the pregnant and lactating females were small in proportion to the mean body weights; also, they were not statistically significant and were transient in nature. However, we agree that the no-effect level for the F_1 pups was 5 mg/kg/day, based on mortality, decreased mean body weight and delay in passive avoidance on PPD 35$\pm$1.

Sidney J. Stolzenberg, PhD

cc:
HFD-120 Division File
HFD-120/LChen
HFD-120/GFitzgerald
HFD-120/AOliva
HFD-120/SStolzenberg
NDA20864.phase4.doc

APPENDIX

Printed by Glenna Fitzgerald

Electronic Mail Message

ty: COMPANY CONFIDENTIAL

Date: 22-Sep-1998 12:14pm
From: Thomas Steele
STEELET
Dept: HFD-120 WOC2 4053
Tel No: 301-594-2850 FAX t-

a Chen (CHENLA)

nna Fitzgerald (FITZGERALD)
a Chen (CHENLA)
ard Fisher (FISHERE)
RE: Maxalt Phase 4 Commitment

arm/tox team (myself, Ed Fisher, and Glenna Fitzgerald) have reviewed the protocol and dose selection proposal for the Maxalt Phase IV commitment dy pre- and postnatal developmental toxicity. The study was recommended Division because postnatal development was not evaluated at sufficiently oses (i.e., evidence of maternal toxicity) in the studies submitted in A The high dose proposed in the submitted protocol (250 mg/kg/day) is the at used in a range-finding study, where it produced an approximate ase in body weight gain. The proposed mid dose (100 mg/kg/day) was in most definitive repro studies in the NDA, and generally produced to minimal maternotoxicity. The proposed low dose (5 mg/kg/day) is ly greater than the NOAEL for F1 (2 mg/kg/day) determined in previous pmental studies. The main parameters to be assessed are developmental, ing neurobehavioral studies. Teratology will not be assessed since the us Seg II studies were acceptable.

lection of doses and study design appear acceptable to address the on's concerns with the previous studies.

NDA 20-864
20-865

Div. File 20-864
20-865

Noted and agree
G97 9/22/98

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	Maxalt
Generic Name:	rizatriptan
Sponsor:	Merck
Indication:	migraine
NDA Number:	20-864 SE8-005
Original Receipt Date:	3/10/00
Clinical Reviewers:	Armando Oliva, MD
Review Author:	Armando Oliva, MD
Review Completed:	7/11/00

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2.7 Reviewer's Conclusion ____ **10**
3. Discussion ____ *10*
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5. Recommendations ____ *12*

1. Background

Maxalt was approved on 6/29/98 for the acute treatment of migraine in adults. This supplemental NDA application contains information to support changes to the approved labeling under the CLINICAL PHARMACOLOGY – Clinical Studies section. The sponsor proposes adding new text indicating that the efficacy of Maxalt was unaffected by relationship to menses, as follows (the added text is underlined):

Clinical Pharmacology – Clinical Studies
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.

The sNDA also fulfills a pre-clinical phase IV commitment. At the time of approval, the Agency requested, and the sponsor committed to conduct an ICH pre- and post-natal developmental toxicity study in rats using doses that produce adequate evidence of maternal toxicity. The submission contains the reports of these studies and the sponsor has revised the appropriate section in the PRECAUTIONS – Pregnancy section of labeling. I do not discuss the results of these pre-clinical studies in this review and refer the reader to the pharm/tox review for additional information.

The rationale for the labeling change is the observation that migraine associated with menses are often more severe, more prolonged, and more difficult to treat. It is therefore important to evaluate the efficacy of rizatriptan in menstrually-associated migraines.

The sponsor admits that menstrual data were not collected in the original phase 3 efficacy studies upon which approval was based. In support of the currently proposed labeling change, the sponsor submits a retrospective analysis of two recently completed efficacy studies (046 and 052) in which data on the menstrual association of migraine was captured. In these trials, a menstrually associated migraine was defined as a migraine attack that occurred ±3 days of the onset of the last menses. The meta-analysis included all female patients in these two trials and the sponsor states that the analysis supports the conclusion that both 5mg and 10mg tablets are effective, compared to placebo, in menstrually-associated migraines. Similar efficacy was observed in menstrually and non-menstrually associated attacks. No new safety issues were identified.

2. Studies 046 and 052

Previously submitted clinical data contained efficacy results from 4 studies using the tablet, and 2 studies using the MLT formulation. None contained menstrual data in females. Since then, two new studies have been conducted – studies 046 and 052. I describe these studies below.

2.1 Protocol

The trial methodology, assessment procedures, and criteria for headache response were similar to the previously submitted trials. Headache was rated on a four point scale (0=none, 1=mild, 2=moderate, 3=severe) and headache response was defined as a reduction in pain from moderate/severe at baseline to mild/no pain at 2 hours. Pain-free was defined as a decrease in severity from moderate/severe pain to no pain at 2 hours.

Both studies were randomized, double blind, placebo-controlled, incomplete block, 2-period, crossover studies that investigated the efficacy and safety of 5mg and 10mg, sumatriptan 25mg and 50mg, and placebo in the treatment of 2 attacks of moderate or severe migraine. Patients treated one attack with rizatriptan and another attack with sumatriptan (or placebo/placebo) in a randomized fashion. Rescue medication was permitted after 2 hours.

In order to have sufficient data to evaluate the efficacy of rizatriptan tablets for the treatment of menstrually-associated migraine, the data sets from both studies were combined. This was the first time that menstrually-associated data were collected in a rizatriptan efficacy trial.

The specific objectives of the analysis were:

- To demonstrate the efficacy of rizatriptan 5mg and 10mg compared to placebo for the acute treatment of menstrually-associated migraine (defined as an attack that occurred ±3 days of onset of the last menstrual period)
- To compare the efficacy of 5mg and 10mg for the acute treatment of non-menstrually-associated migraine

The analysis focused on the subset of female patients in both studies and it used data only for the first attack treated, to avoid any confounding period effect.

In addition to pain severity as described above, the protocols also recorded headache recurrence, functional disability, presence/absence of associated symptoms (nausea, vomiting, photophobia, phonophobia), and the use of rescue. Patients attended three clinic visits and were questioned regarding the date of onset of the last menstrual period.

2.2 Study Population

Table 1 (sponsor table 1, worldwide clinical summary, summary.pdf, page 31) lists the demographic and baseline characteristics for the female patients who participated in both studies. Mean age was about 40 across all groups, and most were white (90-92%). Of the first attack treated, almost 2/3 were moderate and the remaining were severe at baseline. All of these characteristics were reasonably balanced among the various treatment groups.

Table 1: Studies 046 and 052 – Patient Characteristics, Females Only

	Riza 5/ Suma 25		Suma 25/ Riza 5		Riza 10/ Suma 50		Suma 50/ Riza 10		PBO/PBO	
Age										
N	509		495		534		497		376	
Mean	39.8		40.4		40.1		39.7		40.0	
Range	18-71		18-91		18-72		18-68		18-64	
	N	%	N	%	N	%	N	%	N	%
Race										
White	464	91	445	90	481	90	452	91	346	92
Black	27	5	29	6	31	6	24	5	16	4
Other	18	4	21	4	22	4	21	4	14	4
Baseline Severity										
1st Attack										
Mod	299	59	327	66	338	64	294	59	230	61
Sev	207	41	167	34	194	36	201	41	145	39
2nd Attack										
Mod	219	47	251	58	258	53	249	56	183	55
Sev	248	53	182	42	227	47	198	44	152	45

2.3 Efficacy

Using the data from the first attack only, and analyzing all patients, the percentage of patients reporting a headache response and pain-free at 2 hours is shown in Table 2 (sponsor table 2, worldwide clinical summary, summary.pdf, page 33). Also shown are the comparable results from the 4 previous tablet efficacy studies (submitted to the original NDA).

As in the previous four studies, both the 5mg and 10mg tablets were associated with a significantly higher 2-hour headache response rate, when compared to placebo, in both studies. Pain-free rates at 2 hours were also significantly higher in both rizatriptan treatment groups.

Table 2: Maxalt Tablet Two-Hour Headache Response Rates

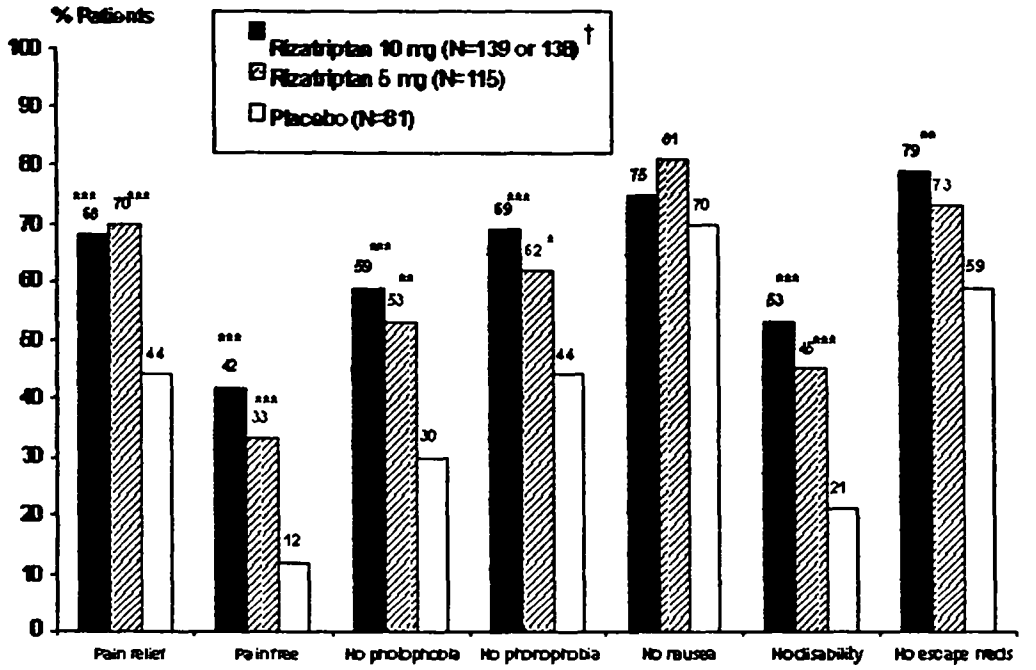
	Protocol Number					
	022	025	029	030	046	052
Response at 2 Hours						
Rizatriptan 10 mg	71%**	77%**		67%**	73%**	66%**
Rizatriptan 5 mg	62%**		63%**	60%**	70%**	64%**
Placebo	35%	37%	23%	40%	38%	41%
Pain-Free at 2 Hours						
Rizatriptan 10 mg	42%**	44%**		40%**	40%**	36%**
Rizatriptan 5 mg	33%**		27%**	25%**	34%**	30%**
Placebo	10%	7%	3%	9%	9%	10%

** $p<0.01$ compared to placebo

The response rates in these two new studies are comparable with those observed in the previous studies.

In the sub-group of females with menstrually-associated migraines (±3 days from onset of menses), the efficacy results of the retrospective pooled analysis is shown graphically in Figure 1 (sponsor figure 1, worldwide clinical summary, summary.pdf, page 34).

Figure 1: Efficacy at Two Hours in Menstrually Associated Migraine Attacks



The 2-hour response rates were 68% and 70% for 5mg and 10mg, respectively, compared with 44% for placebo. This was nominally significant at $p \leq 0.001$. Other efficacy measures also favored the two drug groups (although the no nausea analysis at 2 hours failed to reach nominal significance).

The response rates seen in this subgroup are similar to those seen in the overall study populations (direct comparison with Table 2, above).

The results of this analysis, as well as other secondary analyses, are shown in Table 3

Table 3: Two-Hour Efficacy Results in Women Treating a Menstrual Migraine

Efficacy Measure	Treatment	n/N	%	(95% CI)
Response	Riza 10	94/139	67.6	(59.2, 75.3)
	Riza 5	80/115	69.6	(60.3, 77.8)
	Placebo	36/81	44.4	(33.4, 55.9)
Pain-Free	Riza 10	59/139	42.4	(34.1, 51.1)
	Riza 5	38/115	33.0	(24.6, 42.4)
	Placebo	10/81	12.3	(6.1, 21.5)
No Nausea	Riza 10	104/138	75.4	(67.3, 82.3)
	Riza 5	93/115	80.9	(72.5, 87.6)
	Placebo	57/81	70.4	(59.2, 80.0)

Efficacy Measure	Treatment	n/N	%	(95% CI)
No Photophobia	Riza 10	81/138	58.7	(50.0, 67.0)
	Riza 5	61/115	53.0	(43.5, 62.4)
	Placebo	24/81	29.6	(20.0, 40.8)
No Phonophobia	Riza 10	95/138	68.8	(60.4, 76.4)
	Riza 5	71/115	61.7	(52.2, 70.6)
	Placebo	36/81	44.4	(33.4, 55.9)

In addition to the nominally significant results seen in 2-hour headache response rates and pain-free rates, both doses of rizatriptan were nominally significantly superior to placebo in relieving photophobia and phonophobia at 2 hours. The nausea analysis did not reach nominal significance. The sponsor and I note that the incidence of no nausea at 2 hours in placebo patients was very high at 70%. The sponsor notes that in a subset of patients who had nausea at baseline, rizatriptan 5mg was effective in relieving nausea (66% vs. 59%, $p<0.05$).

The sponsor performed additional analyses, which I don't present here in any detail because I don't believe it adds much to the overall conclusion. They show that the response rates and pain-free rates after treating menstrual and non-menstrual attacks were similar, as were the no nausea, no photophobia, and no phonophobia rates. No significant effect of menses was observed in the incidence of functional disability or the need for escape medications.

2.4 Safety

These two new studies revealed no additional safety concerns that hasn't already been described in product labeling.

There were no deaths. There were five serious adverse events reported in study 046, and all five occurred after treatment with sumatriptan 25mg. There were three serious adverse events in study 052. Two occurred after treatment with rizatriptan 10mg (femur fracture, menstruation disorder), and one occurred after treatment with sumatriptan 25mg (migraine). None was considered treatment-related by the investigator.

Eight patients in study 046 discontinued prematurely due to an adverse event: 5 following treatment with rizatriptan 5 mg (emotional changes, pharyngeal discomfort (2), decreased hematocrit, and migraine), 2 following sumatriptan 25 mg (pharyngeal discomfort, muscle weakness/euphoria), and 1 following sumatriptan 50 mg (4 AE's in the same patient: somnolence/asthenia/dysarthria/decreased mental activity). Three patients in study 052 discontinued prematurely due to adverse events (one each for rizatriptan 5mg – diarrhea and dizziness, rizatriptan 10mg – arm pain and palpitation, and placebo – chest pain).

Somnolence, dizziness, asthenia/fatigue, and nausea were the most common adverse events reported. Clinical adverse events were typically mild or moderate and short-lasting. The incidence of laboratory events was low, and no systematic changes in means scores of laboratory test parameters were observed in migraineurs on placebo or rizatriptan.

The sponsor did not carry out specific safety analyses on the subgroup of menstrual migraine patients since it is not anticipated that the profile would differ between menstrual and non-menstrual attacks. Since the drug is already marketed and the safety profile is well described in approved labeling, I chose not to do an extensive review of the safety data in these studies.

2.5 Sponsor's Conclusions

From the information submitted, the sponsor concludes that, compared to placebo:

- Rizatriptan 5mg and 10mg are effective in the acute treatment of menstrually associated migraine attacks with regard to relief of headache at 2 hours post-dose.
- Rizatriptan 5mg and 10mg are effective at 2 hours post-dose in the treatment of menstrually associated migraine attacks with regard to return to normal function and relief of photophobia and phonophobia. Rizatriptan 10mg tablets are effective at 2 hours post-dose in the reduced need for escape medication. In a subset of patients who had nausea at baseline, rizatriptan 5mg was effective in relieving nausea.

When comparing menstrually-associated migraines to non-menstrually associated migraines:

- Rizatriptan 5mg and 10mg provided similar response rates at 2 hours in both menstrually and non-menstrually associated migraines
- Rizatriptan 5mg and 10mg provided similar efficacy with regard to return to normal function, relief of associated migraine symptoms, and reduced need for escape medication.

With regard to safety:

- Rizatriptan 5mg and 10mg are well tolerated.

2.6 Reviewer's Analysis

The sponsor provided a file that contained efficacy data for all women in both studies. This file is named efficacy.sd2. Each record (row) contained efficacy data at 2 hours for an individual headache. The record also contained baseline headache severity information. A total of 4,822 records were present.

I first deleted those records pertaining to a second attack, and based my analysis on the first attack only. As the sponsor points out, and I agree, this strategy eliminates any period effect as a confounding factor. Exactly half of the records pertained to treatment of a second attack.

There was one patient whose actual dose taken was unknown. I removed her from the analysis. An additional 9 patients had missing baseline headache severity score (1 on placebo, 3 on rizatriptan 5mg, 2 on rizatriptan 10mg, 1 on sumatriptan 25mg, and 2 on sumatriptan 50mg). I also removed them from the analysis. This resulted in 2,401 patients for analysis. Of note, all remaining patients had baseline headache scores of either 2 (moderate) or 3 (severe).

The sponsor provided a variable called "Menstruation Flag (1=Yes)" to identify a menstrual migraine. I requested and subsequently received the actual date that menses

began (MENSDATE) and the date the migraine was treated (DOSEDATM). I agree with the sponsor that the treatment date is ostensibly equivalent to the date that the migraine occurred. If the headache was treated ±3 days from menses onset, then I identified it as a menstrual migraine. I compared my list of menstrual migraines with the one provided by the sponsor. Our lists were identical with the exception of 3 patients in study 46 whom the sponsor had identified as having unknown menstrual status at the time of their migraine, whereas, according to my calculation, they clearly treated a menstrual migraine based on the definition described above. I treated them as menstrual migraines for all further calculations. The distribution of the 2,401 women were as follows. I use "RA" to designate a reviewer-analysis generated table.

Table 4 (RA): Distribution of Female Patients

Study	Total	PBO	Rizatriptan 5mg	Rizatriptan 10mg	Sumatriptan 25mg	Sumatriptan 50mg
46	1158	124	256	275	254	249
non MM	*880*	*91*	*200*	*202*	*196*	*191*
MM	*278*	*33*	*56*	*73*	*58*	*58*
52	1243	251	250	255	240	247
non MM	*950*	*203*	*191*	*189*	*181*	*186*
MM	*293*	*48*	*59*	*66*	*59*	*61*
Total	**2401**	**375**	**506**	**530**	**494**	**496**

MM=menstrual migraine (±3 days from onset of menses)

I defined a responder at 2 hours as a patient who had a moderate/severe headache at baseline and a mild/no headache at 2 hours.

The percent responders for each group is shown in Table 5. I do not provide p-values since this is a purely descriptive, retrospective analysis.

Table 5 (RA): Two-Hour Response Rates

Study	PBO	Rizatriptan 5mg	Rizatriptan 10mg	Sumatriptan 25mg	Sumatriptan 50mg
46	48/124 (39%)	182/256 (71%)	197/275 (72%)	156/254 (61%)	173/249 (69%)
non MM	*30/91 (33%)*	*142/200 (71%)*	*142/202 (70%)*	*124/196 (63%)*	*130/191 (68%)*
MM	*18/33 (55%)*	*40/56 (71%)*	*55/73 (75%)*	*32/58 (55%)*	*43/58 (74%)*
52	98/251 (39%)	156/250 (62%)	165/255 (65%)	148/240 (62%)	171/247 (69%)
non MM	*80/203 (39%)*	*117/191 (61%)*	*126/189 (67%)*	*113/181 (62%)*	*128/186 (69%)*
MM	*18/48 (38%)*	*39/59 (66%)*	*39/66 (59%)*	*35/59 (59%)*	*43/61 (70%)*

MM=menstrual migraine (±3 days from onset of menses)

This table shows that all four active treatment groups had numerically higher response rates compared to placebo in both studies. The response rates in the subset of menstrual migraines in each study were higher for all active drug groups compared to placebo, were comparable to the overall response rates for the entire treatment group for the respective

study, and were similar to the response rates in the subgroup of non-menstrual migraines. This appeared to be true for both rizatriptan and sumatriptan.

2.7 Reviewer's Conclusion

I conclude from the data presented that the efficacy of rizatriptan 5mg and 10mg appears to be unaffected by relationship to menses. There are no new safety concerns raised by these two new studies.

3. Discussion

With regard to the proposed new statement that clinical efficacy was unaffected by relationship to menses, a bit of historical perspective regarding previous triptan applications is important in order to decide whether such a statement should be allowed.

There are at present four approved triptans:

- Sumatriptan (injection, tablet, nasal spray)
- Zolmitriptan (tablet)
- Naratriptan (tablet)
- Rizatriptan (tablet, orally disintegrating tablet)

I reviewed the labeling of all triptan products to see whether such a statement is already present in other products. Of all the triptans, only zolmitriptan and sumatriptan tablet labeling already contain a similar statement. Therefore, a similar change in Maxalt labeling can be allowed, if true, in order to maintain consistency. The corresponding sections in labeling of the triptans are listed below.

Sumatriptan injection
The efficacy of IMITREX Injection is unaffected by whether or not migraine is associated with aura, duration of attack, gender or age of the patient, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers).

Sumatriptan tablet
The efficacy of IMITREX Tablets was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the patient; relationship to menses; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

Sumatriptan nasal spray
The efficacy of IMITREX Nasal Spray was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the patient; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

Zolmitriptan tablet
The efficacy of ZOMIG was unaffected by presence of aura; duration of headache prior to treatment; relationship to menses; gender, age or weight of the patient, pretreatment nausea or concomitant use of common migraine prophylactic drugs.

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

Rizatriptan tablet/orally disintegrating tablet (one label)
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.

4. Labeling Review

I do not discuss the pre-clinical sections of labeling, and refer the reader to the pharm/tox review for this information. The sponsor proposes the following changes to the clinical pharmacology section.

Clinical Pharmacology – Clinical Studies
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.

I don't recommend separating out the corresponding Maxalt statement in a separate paragraph since it gives the results undo weight and importance. This is not justified given the fact that the conclusion come from a retrospective, subgroup analysis. However, it is not appropriate to include it in the original list of covariates, since it implies that the menstrual status was captured in the original four efficacy studies upon which approval of rizatriptan was based. Instead, I recommend the following statement. It differs from the corresponding text in that it makes it clear that the data on menstrual migraine come from two new (not previously described) studies:

Clinical Pharmacology – Clinical Studies
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.

5. Recommendations

I recommend approval of the efficacy supplement with the changes to existing labeling, as described in the previous paragraph.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. /S/

ao 7/11/00
cc:
HFD-120
NDA 20-864 SE8-005

NDA 20-864 S-004 Maxalt Tablets
NDA 20-865 S-005 Maxalt MLT Orally Disintegrating Tablets

We agree with your proposed changes for the WARNINGS:cerebrovascular events section and the PPI. However, we ask that you further revise the following sections:

1. WARNINGS section

Current and/or Proposed Labeling:

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 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.

FDA Proposal:

Cardiac Events and Fatalities Associated with 5-HT_1 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 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. 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.

2. ADVERSE REACTIONS section

Proposed Labeling:

FDA Proposal:

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.
Cerebrovascular: stroke.
Special Senses: dysgeusia.

NDA 20-864 S-005 Maxalt Tablets
NDA 20-865 S-006 Maxalt MLT Orally Disintegrating Tablets

We ask that you further revise the following sections:

1. CLINICAL PHARMACOLOGY:Clinical Studies section

Proposed Labeling:

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.

FDA Proposal:

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.

2. PRECAUTIONS:Pregnancy section (1st paragraph)

Proposed Labeling:

Pregnancy: Pregnancy Category C

FDA Proposal:

Pregnancy: Pregnancy Category C

In a general reproductive toxicity 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 exposures 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 500 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.

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-864 (SLR-007) 20-865 (SLR-007)**
Sponsor:	**Merck**
Drug:	**Maxalt and Maxalt MLT**
Proposed Indication:	**migraine**
Material Submitted:	**Labeling Changes Being Effected**
Correspondence Date:	**11/2/00**
Date Received / Agency:	**11/3/00**
Date Review Completed	**11/22/00**
Reviewer:	**Armando Oliva, MD**

1. Introduction

These submissions contain changes being effected that are intended to strengthen the labeling of the approved products. Since Maxalt and Maxalt-MLT share the same product labeling, the proposed changes are submitted to both NDA's.

2. Changes to Labeling

The sponsor proposes adding the following text to the Adverse Reactions, Post-Marketing Experience section:

Skin and Skin Appendages: Toxic Epidermal Necrolysis (TEN).

3. Justification for Labeling Change

The sponsor has not provided any justification for the labeling change. I do not know how many cases they have of TEN associated with Maxalt use, nor do I know any details of any of the cases.

4. Comments

I concur that these proposed changes do strengthen the labeling to promote the safe use of the drug. For that reason, I recommend we approve the supplement. However, because they have failed to provide details about the cases of TEN that led to this change, we should request they submit this information. I think it can be done post-approval. Upon review of the actual cases, it is possible that we may want to recommend additional changes (*e.g.* to the warnings or precautions section(s)) depending on the results of that review. The sponsor should be made aware of this possibility.

The following may be conveyed to the sponsor:

1. Please submit documentation of all reported cases of toxic epidermal necrolysis (TEN).
2. After our review of this information, it is possible that we may request additional labeling changes.

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. (S)

ao 11/22/00
cc:
HFD-120
NDA 20-864 (SLR-007) 20-865 (SLR-007)

/s/

Armando Oliva
11/22/00 03:01:41 PM
MEDICAL OFFICER

hard copy is in your inbox 11/22/00

Russell Katz
11/28/00 08:16:21 AM
MEDICAL OFFICER
I have discussed this Dr. Oliva. We agree that the supplement cannot be approved until the information about the cases is submitted. The information will be requested. The supplement does qualify as a CBE, however.

DRAFT

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-864 (SLR-007) 20-865 (SLR-007)**
Sponsor:	**Merck**
Drug:	**Maxalt and Maxalt MLT**
Proposed Indication:	**migraine**
Material Submitted:	**Labeling Changes Being Effected**
Correspondence Date:	**11/2/00**
Date Received / Agency:	**11/3/00**
Date Review Completed	**12/4/00**
Reviewer:	**Armando Oliva, MD**

1. Introduction

These submissions contain changes being effected that are intended to strengthen the labeling of the approved products. Since Maxalt and Maxalt-MLT share the same product labeling, the proposed changes are submitted to both NDA's. This review is an amendment to my original review of these submissions, dated 11/22/00. In that review, I agreed that the proposed change qualified as a CBE.

The sponsor has proposed an addition to the Adverse Reactions, Post-Marketing Experience section to add the following reaction to the list:

Skin and Skin Appendages: Toxic Epidermal Necrolysis (TEN).

However, in the submission, they did not provide the case(s) on which they rely for the change. Mr. Nighswander, our project manager, contacted the sponsor by phone and was informed that they have only one case, and that case was submitted separately to OPDRA some months ago. They have faxed the details of the case for me to review, which I describe below.

I spoke with Charlene Flowers, at OPDRA, and it turns out that she is aware of the case. Furthermore, she has searched AERS for additional cases, and has not found any. Also, she has discussed this case with her European counterparts, and they are aware of no additional cases.

2. Single Case of TEN

The case in question involves a 23 year old female in the Netherlands who took a single tablet of Maxalt orally disintegrating tablet (MLT) 10mg on 10/27/1999 for the treatment of a migraine. She experienced headache, diarrhea, urticaria, exanthema, pain and facial swelling. Maxalt was discontinued. On 1/1/2000, she developed toxic epidermal necrolysis. No information is provided during the period 12/27 and 1/1. In particular, we do not know whether her initial symptoms resolved/improved prior to the onset of TEN on 1/1, or whether the TEN resulted from a gradual worsening of her initial symptoms. She was hospitalized on —— with TEN over 24% of her body, including conjunctivitis, stomatitis, and vulvitis. Two biopsies confirmed the diagnosis of TEN.

She was treated with flammazine, infusion solutions, oxygen, and morphine. On ——— were almost completely resolved and she was discharged on — — The referring physician felt her symptoms were related to treatment with rizatriptan.

3. Comments

1. I agree that the incident should be added to labeling. The temporal aspects of the case make it likely that is was treatment-related. The incident clearly was serious. It resulted in hospitalization. Since it is only one case, and the subject appeared to recover without sequelae, I agree to their proposal to list the event in the post-marketing section of Adverse Events. We should remain on alert for any additional cases, which may then necessitate a stronger action.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. /S/

ao 12/4/00
cc:
HFD-120
NDA 20-864 (SLR-007) 20-865 (SLR-007)

COMPLETED NOV 30 2000

NOV 30 2000

STATISTICAL REVIEW AND EVALUATION

NDA : 20-864/SE8-005

Name of Drug : MAXALT® Tablets

Indication : Menstrual association of migraine attacks

Sponsor : Merck Research Laboratories

Medical Reviewer : Oliva Armando, M.D.

I. BACKGROUND

This supplemental NDA application is to revise the labeling claim on the menstrual association of migraine attack based on a retrospective meta-analysis of two clinical studies (protocols 046 and 052) where the menstrual data were retrospectively collected. Since the effect on menses related migraine was not indicated in the original labeling, the sponsor wants to mention that "efficacy was unaffected by relationship to menses" in the proposed labeling claim.

The two studies used here were originally planned to support the promotional claims and were not planned for this particular supplemental NDA submission. Therefore the primary endpoint(s) and the primary comparison proposed in the original protocols do not agree with the endpoint and comparison used in this submission. Since this submission involves subgroup of patients (i.e. females with or without menstrual related migraine), the sponsor used the combined data from the two studies to get an "adequate" number of patients for the analysis. Since the sponsor's submission was based on the combined datasets, this reviewer will not provide detailed summary for each individual study. But the compatibility of the two studies, the evolution of utilizing the menstrual related migraine data and the related statistical issues will be discussed.

The sponsor's analysis was based on the post-hoc analyses and there was no pre-specified statistical decision rule, so such analysis can only be treated as an exploratory analysis. Any results from such analysis should be interpreted with caution.

II. PROTOCOL 046 AND 052

The primary therapy period for protocol 046 was from October 1996 to June 1997; while it was from December 1997 to May 1998 for protocol 052. Protocol 046 had one amendment dated December 23, 1996.

II.1 Design

Both studies are incomplete block, two-period crossover, double-blind (with in-house blinding), placebo-controlled, outpatient study. In the studies, each patient received a single-dose acute oral treatment for each of two acute moderate/severe migraine attacks, which were separated by at least 5 days. The headache II treatment was not allowed until patients had completed the interim study visit.

The detailed treatment regimens were displayed in tables I.1 for both protocols 046 and 052.

Table I.1 The Treatment Regimens by Period

Treatment group	Attack 1	Attack 2
1a	5mg rizatriptan placebo + 50mg sumatriptan placebo	5mg rizatriptan placebo + 50mg sumatriptan placebo
1b	**5mg rizatriptan** + 50mg sumatriptan placebo	**25mg sumatriptan** + 5mg rizatriptan placebo +25mg sumatriptan placebo
1c	**25mg sumatriptan** + 5mg rizatriptan placebo +25mg sumatriptan placebo	**5mg rizatriptan** + 50mg sumatriptan placebo
2a	10mg rizatriptan placebo + 50mg sumatriptan placebo	10mg rizatriptan placebo + 50mg sumatriptan placebo
2b	**10mg rizatriptan** + 50mg sumatriptan placebo	**50mg sumatriptan** + 5mg rizatriptan placebo
2c	**50mg sumatriptan** + 5mg rizatriptan placebo	**10mg rizatriptan** + 50mg sumatriptan placebo

Note : Bolded phases indicate active treatments

The sponsor noted that since rizatriptan 5 mg tablets were smaller than the higher-dose tablets, the blinding of the rizatriptan doses may be compromised (i.e. patients can tell whether they are in group 1 or 2). So they packaged the supplies in opaque containers to prevent patient or staff from doing cross-patient comparison and they also instructed the patients and the investigation staff not to compare the study medication with others, nor to ask the patient about the appearance of the medication. They also noted that the Sumatriptan 25-mg and 50-mg tablets and its corresponding tablets are identical in appearance.

The planned sample sizes and the number of sites for both studies were summarized in Tables I.2. As indicated in this table, a change of sample size for study 046 was shown, but no rationale of the change was documented.

Table I.2
Planned Sample Sizes and Number of Centers

Protocol 046		Protocol 052	
Protocol dated August 15, 1996	Enrolled 1170 patients, 45 U.S. sites 900 evaluable patients: Group 1b,1c : n=400 Group 2b,2c : n=400 Group 1a+2a : n=100	Protocol dated September 18, 1997	Enrolled 1170 patients, 75 U.S. sites 1200 evaluable patients: Group 1b,1c : n=480 Group 2b,2c : n=480 Group 1a+2a : n=240
Amendment dated December 23, 1996	Enrolled 1530 patients, 45 U.S. sites 1170 evaluable patients: Group 1b,1c : n=520 Group 2b,2c : n=520 Group 1a+2a : n=130		

Patients who did not respond (i.e. achieved mild or no pain) at hour 2 post-dose would be permitted to take escape medication at that time and additional analgesia thereafter if the headache did not resolve. Patients who had recurrent headache (defined as a return, within 24 hours postdose of moderate to severe headache in patients who responded at hour 2) were also allowed to take escape medication.

II.2 Efficacy Endpoints

The primary efficacy measures for both studies are headache severity rating (grades 0 to 3 = no pain, mild, moderate, or severe) at baseline and at a 0.5 hour interval up to 2-hour after dosing. The primary efficacy endpoint was pain relief defined as a reduction in headache pain from moderate/severe at baseline to mild or no pain 2 hours after dosing.

Additional measures included headache severity rating at 3 and 4 hours post-dose; presence or absence of associated symptoms: nausea, vomiting, photophobia, phonophobia; functional disability rating (0=normal; 1=mild impaired; 2= severely impaired; 3=unable to carry out daily activity, require bed rest); the incidence of headache recurrence and collection of the date of onset of the last menstrual period, etc.

The collection of the last menstrual period date was not indicated in the original 046 study and was added to the protocol in the December 23, 1996 amendment after starting of the study.

The efficacy parameters indicated in the sponsor's post-hoc statistical report are :

1. Pain relief at 2 hours (headache severity = 0 or 1)
2. Pain free at 2 hours (headache severity =0)
3. No Nausea at 2 hours

4. No Vomiting at 2 hours
5. No photophobia at 2 hours
6. No phonophobia at 2 hours
7. No functional disability at 2 hours
8 Use of escape medication within 24 hours
9. Recurrence within 24 hours

II.3 Objectives

The primary objective for protocol 046, originally, (in the original protocol dated August 15, 1996) was

1) To compare rizatriptan, averaged across doses, with sumatriptan in time to headache relief up to 2 hours pose-dose;
2) To compare rizatriptan 5 mg and 10 mg with placebo in the proportion of patients achieved pain relief at 2 hour post-dose.

In the December 23, 1996 amendment, the primary objectives were read as

1) To compare rizatriptan 10 mg to sumatriptan 50 mg in terms of time to headache relief up to 2 hours post-dose;
2) To compare rizatriptan 5 mg and 10 mg to that of placebo in the proportion of headache relief at 2 hours post-dose.

Th primary objective of protocol 052 (dated September 19, 1997) was the same as the objective 1) of protocol 046. The co-primary objective 2) of protocol 046 was treated as a secondary objective in protocol 052

The comparison of active treatments to placebo with respect to the proportion of patients achieved pain relief in female with menstrually-associated migraine attack at 2 hours was not mentioned in the original protocol 46 (August 15, 1996), but was later added in the protocol amendment (December 23,1996). The menstrually-associated migraine attack was defined as the migraine attack occurring within –3 to +3 days of the onset date of the last menstrual period.

This comparison of the menstrually-associated migraine attack between active treatments and placebo was included in the original protocol 52 as the secondary endpoint. In both studies, exploratory analyses were done to evaluate the treatment effect on menstrually-associated migraine.

In this submission, the co-primary objective 2) of protocol 046 was treated as the primary objective. Furthermore, the effect of menstrually-associated migraine attack was now incorporated into the primary objective. The primary objectives specified in this post-hoc analysis were :

1) To demonstrate the efficacy of rizatriptan 5- and 10-mg tablet compared to placebo for the treatment of menstrually-associated migraine attacks,
2) To compare the efficacy of rizatriptan 5- and 10-mg tablet for the treatment of Nonmenstrually-associated migraine attacks to menstrually-associated migraine attacks.

II.4 Post-Hoc Analysis Plan

In the sponsor's post-hoc analysis summary, only results from the first treated headache were reported. The sponsor claimed that the treatment effect may be confounded by the period-dependent factor, such as the menstrually-related migraine, if both attacks were used. However, both attacks were analyzed in the statistical report.

In addition, the sponsor's post-hoc analysis only involved female patients in groups 1a, 1b, and 2a, 2b (i.e. exclude group 1c and 2c which was assigned to take sumatriptan for headache I). This review will focus on the relevant methods used for the primary comparison based on the combined datasets which involved female patients using rizatriptan or placebo to treat the migraines.

One of the rules specified in the Data analysis section of the two individual protocols was used for all analyses.

- For comparisons between rizatriptan and placebo, placebo subgroups (groups 1a and 2a) was combined if the difference between the two placebos in the proportion of patients achieved pain relief at 2 hours is not significant at 0.05 level. Otherwise, the comparison was based on comparing the matched placebo dose levels.

Since no difference in two placebo subgroups found in each individual study, these two groups were combined in the post-hoc analysis

An "all patient treated" population was used for the primary efficacy analysis in both study reports. The "all patient treated" population is similar to the intent-to-treat population which was defined as all patients who took study medication and had at least one efficacy measurement after the initial dose. In the post-hoc analysis, the "all patients treated" was restricted to female patients.

In the sponsor's statistical report, two subsets of the "all patient treated" population were used for the primary efficacy analysis based on two objectives mentioned in the earlier section :

1) Subset 1 : All female patients who either had menstrually-related or non-menstrually-related migraine attack and were treated with rizatriptan or placebo were included.

2) Subset 2 : Only female patients who had the first menstrually associated migraine attack and were treated with rizatriptan or placebo were included.

Logistic regression models including treatment, study and menstrual association (yes/no) as main effects and a separated interaction term (will be specified in the following steps) were used to analyze Subset 1.

Two interaction terms were incorporated into the logistic regression model **separately** in the following order:

1) Test study by treatment interaction : this test was used to test the "poolability" of two studies using a significance level of 0.05. If this test is significant, the pooling of the studies would not be appropriate.
2) Test menstrual association by treatment interaction : A significant effect (<0.05) would indicate that the treatment effect is different between the menstrual associated migraines and non-menstrual associated migraines. A further exploratory analysis will be performed to evaluate the interaction.

Assuming the interaction terms in steps 1) and 2) are not significant, the logistic regression model including treatment, study and menstrual status **without interaction** will be used to test menstrual association (i.e. the effect of menstrual status). If the effect of menstrual status is significant, it would indicate that the proportion of responders was different in the menstrually-associated migraines and non-menstrually-associated migraines.

The analysis method used for subset 2 was based on logistic regression including treatment and study as two factors. Since treatment by study interaction was not significant (it was confirmed by this reviewer), no interaction term was included in this analysis.

Last-observation-carried-forward (LOCF) technique was used to estimate the missing values. No imputation was made for missing baseline or 0.5-hour values.

III. SPONSOR'S RESULTS

Approximately 89% of the total treated patients for attack 1 from groups 1a+2a, 1b and 2b are females (1413 out of 1606). Table II.1 shows the numbers of female patients with migraine attacks on each period, by study and treatment group (for groups 1a+2a, 1b and 2b).

Table II.2 shows the numbers of menstrually-associated migraine attacks by study and treatment. The results show that the percentages of menstrually-associated first migraine attacks combined treatment groups for the two studies are close (24.4% and 23.1% for studies 046 and 052, respectively).

Table II.3 presents the baseline patient characteristics by treatment group. The mean age and racial distribution are similar across different treatment groups. The distribution of the baseline headache severity also seems comparable between treatment groups But since no menstrually-associated baseline migraine pain severity was analyzed, the comparability of the baseline pain severity between treatment groups with respect to each menstrual status (menstrually-associated or non-menstrually-associated) can not be determined from this table.

Table II.1 Numbers of Female Patients Treated by treatment group *

Protocol No.	Attacks	Riza 5mg	Riza 5mg	Placebo	Total
046	First	256	275	124	655
	Second ¥	228	231	108	567
052	First	250	257	251	758
	Second ¥	205	216	227	648
Combined	First	506	532	375	1413
	Second ¥	433	447	335	1215

Note : * only attacks with non-missing data are included here
¥ Based on results from the second period of groups 1c and 2c.

Table II.2 Numbers of Female Patients with Menstrually Associated Migraine attacks

Treatment	Protocol No.	Attack 1			Attack 2 *		
		N	n	%	N	n	%
Riza 5mg	046	256	55	21.5	228	49	21.5
	052	250	60	24.0	205	35	17.1
	Combined	506	115	22.7	433	84	19.4
Riza 10mg	046	275	72	26.2	231	48	20.8
	052	257	67	26.1	216	50	23.2
	Combined	532	139	26.1	447	98	21.9
Placebo	046	124	33	26.6	108	14	13.0
	052	251	48	19.1	227	38	16.7
	Combined	375	81	21.6	335	52	15.5
Total	046	655	160	24.4	567	111	19.6
	052	758	175	23.1	648	123	19.0
	Combined	1413	335	23.7	1215	234	19.3

Note : N=Number of female patients treating attacks;
n=Number of attacks which were associated with menstrual period.
* Based on results from the second period of groups 1c and 2c.

Table II.3 Baseline Patient Characteristics by Treatment Group (Protocol 046 and 052 combined, Female Patients Only)

Baseline Characteristics	Riza 5mg (N=509)		Riza 10 mg (N=534)		Placebo (N=376)	
Age: N	509		534		376	
Mean	39.8		40.1		40.0	
Range	(18, 71)		(18, 72)		(18, 64)	
	N	%	N	%	N	%
Racial Origin:						
Caucasian	464	91	481	90	346	92
Black	27	5	31	6	16	4
Other	18	4	22	4	14	4
Baseline Headache Severity						
First Attack						
Moderate	299	59	338	64	230	61
Severe	207	41	194	36	145	39
Second Attack *						
Moderate	251	58	249	56	183	55
Severe	182	42	198	44	152	45

Note : * Based on results from the second period of groups 1c and 2c.

Table II.4 Summary of Results From the Logistic Regression Model Analysis of Attack 1 Data

Parameters	p-values		Menstrual Association*	
	Study-by-Treatment Interaction	Menstrual-by-Treatment Interaction	Odds Ratio(95% CI)	p-Value
Pain relief	0.362	0.606	1 1 (0.9, 1.4)	0 418
Pain free	0.912	0.745	1.2 (0.9, 1.6)	0.162
Functional disability	0.915	0.804	1.2 (0.9, 1.5)	0.190
Photophobia	0.838	0.846	1.0 (0.8, 1.2)	0 785
Phonophobia	0 634	0.663	1.1 (0 8, 1.4)	0.696
Nausea	0.095	0.273	1.2 (0.9, 1.6)	0.175
Vomiting	0.004	0.841	1.1 (0.5, 2.5)	0.794
Escape medication	0.043	0.844	1.0 (0.8, 1.3)	0.995

Note: This analysis included rizatriptan and placebo groups.
* Odds ratios and p-values from logistic model with main effects of treatment, study, and menstrual association

The analysis results for subset 1 were presented in Table II.4. In general, the interaction terms were not significant at 0.05 level, except the study by treatment interactions for vomiting and the use of escape medication. The sponsor pointed out that the study by treatment interaction was quantitative, not qualitative since rizatriptan was superior to placebo in both studies based on a visual inspection of the data plot. They indicated that

the finding could justify the pooled analysis for both vomiting and the use of escape medication.

Since no significant menstrual by treatment interaction, the sponsor concluded that the treatments are equally as effective in menstrually associated migraines as in non-menstrually associated migraines.

In the results from the logistic model analysis including only main effects of treatment, study, and menstrual status, no statistical significance was found for the effect of menstrual status. Since all the odds ratios between two menstrual status are all above 1 or equal to 1, the sponsor stated that "the odds ratios indicated that the probability of response in a menstrually-associated attack is about the same as in a non-menstrually associated attack".

The results based on the subset of menstrually-related migraines were presented in Table II.5. The sponsor summarized that rizatriptan was numerically superior to placebo since the odds ratios were all >1.0. However, the sponsor did not mention that the treatment effect for nausea and vomiting did not achieve the statistical significance Instead, the sponsor acknowledged that the small sample size had caused a high variability which was reflected in some large confidence interval for the odds ratios

Since the post-hoc analysis was based on a secondary endpoint and a subgroup of patients (females), the sponsor noted a possible loss of power in detection the treatment effect on menstrually-associated migraines. They conducted a post-hoc power calculation and concluded that the post-hoc analysis had 80% power to detect a difference of 6 percentage points (e.g. 65% versus 71%) for menstrual versus nonmenstrual association, assuming alpha of 0.05 and a two-tailed test.

Table II.5 Summary of Results From the Analysis of Menstrually Associated Migraine Attacks

		Riza 5 mg vs. Placebo			Riza 10 mg vs Placebo		
Parameter	Attack	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p-Value
Pain relief	1	2.8	(1.6, 5.1)	<0.001	2.5	(1 4, 4.5)	0.001
	2	3.4	(1.6, 7.1)	0.001	4.7	(2.3, 9.7)	<0.001
Pain free	1	3.5	(1 6, 7.5)	0 001	5.2	(2.5, 10.9)	<0.001
	2	1.6	(0.7, 3.8)	0.301	3.0	(1.3, 6.9)	0.009
No functional disability	1	3.1	(1.6. 5.9)	<0.001	4.2	(2.2, 7.9)	<0 001
	2	2.1	(1.0, 4.8)	0.066	3.2	(1.5, 7.1)	0.003
Photophobia	1	2.6	(1.4, 4.8)	0.002	3.3	(1 8. 5.9)	<0.001
	2	2.1	(1 0, 4.4)	0.058	2 6	(1.3, 5.3)	0.010
Phonophobia	1	2.0	(1.1, 3.5)	0.021	2.7	(1.5, 4.7)	<0 001
	2	2.0	(1.0, 4 0)	0 064	2.3	(1.2, 4 7	0.017
Nausea	1	1.7	(0.9, 3 4)	0.108	1.2	(0 7, 2 3)	0.520
	2	2.2	(1.0, 4 7)	0.050	2.5	(1.2, 5.3)	0.018
Vomiting	1	2.2	(0.4, 13 7)	0.386	1 8	(0 4, 9 1)	0 482
	2	3 4	(0.3, 39 7)	0.325	2 0	(0 3, 14.5)	0 513
Use of escape medication	1	1.8	(1.0, 3.4)	0.050	2.5	(1.4, 4.7)	0.002
	2	1.9	(0.9. 3.9)	0 087	3 7	(1 7, 7 9)	<0 001

Note Only menstrually associated migraine attacks are included in this analysis.
The sample sizes were as follows

Attack 1:	Riza 5 mg	115	Attack 2: Riza 5 mg	84
	Riza 10 mg	139	Riza 10 mg	98
	Placebo	81	Placebo	52

IV. REVIEWER'S EVALUATION AND COMMENTS

This reviewer had confirmed the sponsor's analysis results based on the primary and some secondary efficacy endpoints (i.e. pain relief and pain free response, proportions of patients with no photo- and phonophobia, no vomiting, no nausea as presented in the previous section) using the sponsor submitted data. In general, the statistical significance difference of treatment effect in menstrually- and non-menstrually-related migraines can not be confirmed based on these endpoints. Also, for most of these endpoints, the significant treatment effects for the menstrually-related migraine was achieved. But, no significant treatment effects for nausea and vomiting were shown for the menstrually-related migraine.

In general, the baseline severity and symptom scores between the menstrually and non-menstrually associated migraines were comparable. However, the reviewer noticed that the patients with non-menstrually associated migraine were older than those with menstrually related migraine. The results were shown in Table III.1.

This reviewer was not convinced that the analyses provided confirmatory finding. One of the primary reasons is that the results were based on post-hoc finding. The primary endpoint and analysis were not pre-specified. There were no rigorous decision rule put in advance. In addition, this reviewer found that the pooling study scheme was not fully convincing. Since the demonstration of no significant study by treatment interaction can only be interpreted as that the interaction can not be confirmed, not there was no interaction.

Another reason that supports this reviewer's concern is that the proposed labeling claim relied upon the results of not rejecting the null hypotheses (i.e. treatment by menstrual status interaction and menstrual association are not significant). Not rejecting the null hypothesis did not provide the evidence of no menses association of the drug efficacy. The result can only be interpreted as that the relationship of the drug efficacy and the menstrual status can not be confirmed.

Two additional reasons also support this reviewer's view. First, the menstrual status was highly correlated with the age group. To demonstrate this point, age was dichotomized based on 50-year-old as the cut-off point. A Cochran Mantel Haenszel test was performed to test the association of menstrual status and age group, adjusting for study. A highly significant p-value was obtained (<0.0001) which indicates strong association between of the menstrual status and age group. The results showed that for protocol 046 and 052, 29% and 27% of the menstrual related migraines are from younger population (<50 years), while only 4% and 6% of such migraines are from older population ($\geq$ 50 years) (Table III.2). The results were not changed when the age cut-off point was decreased to 45-year-old.

This significant association confirms the notion that the younger patients had higher percentage of menstrual related migraine. From this result, age can be considered as a confounding factor to menstrual status. Without further investigation, the treatment effect of menstrually and non-menstrually related migraines can not be fully understood based on current study.

The second reason of why the analysis results can not be considered as a confirmatory finding is that the power to test the interaction term was typically very low. The sponsor's main objective in this supplemental NDA is to claim that there was no difference in treatment effect in menstrually and nonmenstrually related migraines. So, the main objective is to test the null hypothesis that there was no treatment by menstrual migraine status interaction.

This reviewer did not come up with the same post-hoc power calculation result as shown by the sponsor. Instead, this reviewer obtained a result that shows, approximately, a total sample size of 1895 (not the total treated females patients presented in the study: n=1413) was needed to detect a difference of 6 percent (65% versus 71 %) for menstrual versus non-menstrual association with 80 % power (used a two-proportion sample size calculation formula from Fleiss, 1981).

The assumption for the post-hoc power calculation used by the sponsor had over simplified the scenario. The sponsor assumed the response rates were 65% versus 71% for the menstrually and non-menstrually related migraines, respectively. However, the primary objective of this study is to test whether the treatment effect (i.e. rizatriptan versus placebo) was different between the menstrually- and non-menstrually-related migraine. Should the treatment by menstrual status interaction have been tested, the power calculation based on the current sample size would be even smaller than what the sponsor had achieved This low power resulted from the current study provided additional indication of why the sponsor's analysis can not be considered as confirmatory.

Table III.1 Baseline Patient Characteristics, Pain Severity and Symptom Scores by Menstrual associated Migraine and Treatment Group (Protocol 046 and 052 combined, Female Patients Only)

Baseline Characteristics		Riza 5mg (N=509)		Riza 10 mg (N=534)		Placebo (N=376)	
Age:							
Mens.	N	115		139		81	
	Mean (SD)	37.0 (7.66)		35.9 (8.59)		36.7 (8.63)	
	Range	(52,18)		(54,18)		(55,19)	
Non-Mens:	N	391		393		294	
	Mean (SD)	40.7 (9.88)		41.6 (10.33)		40.8 (10.41)	
	Range	(71,19)		(72,19)		(64,18)	
		N	%	N	%	N	%
Racial Origin:							
Mens.	Caucasian	357	91.3	351	89.3	269	91.5
	Black	20	5.1	26	6.6	14	4 8
	Other	14	3.6	16	4.1	11	3.7
Non-Mens.	Caucasian	104	90.4	128	92.1	77	95.1
	Black	7	6.1	5	3.6	2	2.5
	Other	4	3.5	6	4.3	2	2.5
Pain severity							
Mens	Moderate	66	57 4	91	65.5	55	67.9
	Severe	49	42.6	48	34.5	26	32.1
Non-Mens	Moderate	233	59 6	247	62.9	175	59.5
	Severe	158	40 4	146	37.2	119	40 5
No photophobia							
Mens.	Present	14	12.2	11	8.0	12	14.8
	Not-present	101	87 8	127	92.0	69	85.2
Non-Mens.	Present	51	13.0	61	15.6	46	15.7
	Not-present	341	87.0	331	84 4	248	84 4
No phonophobia							
Mens.	Present	31	27.0	31	22 5	14	17.5
	Not-present	84	73.0	107	77.5	66	82.5
Non-Mens.	Present	95	24 6	96	24 5	80	27.3
	Not-present	291	75.4	296	75.5	213	72.7
No nausea							
Mens.	Present	41	35.7	68	49.3	37	46.3
	Not-present	74	64.4	70	50.7	43	53.8
Non-Mens.	Present	139	36.2	168	43.0	101	34 6
	Not-present	245	63.8	223	57.0	191	65.4
No vomiting							
Mens.	Present	106	93.0	133	96 4	79	98.8
	Not-present	8	7.0	5	3.6	1	1.3
Non-Mens.	Present	365	95.3	368	94.9	271	93.8
	Not-present	18	4 7	20	5.2	18	6.2

Table III.2 Menstrual Association Status and Age group (<50, ≥ 50), by Protocol

Protocol Age	Menstrual Status	N	%
046			
<50.	Mens.	155	28.7
	Non-Mens	386	71.4
≥ 50	Mens.	5	4.4
	Non-Mens.	109	95.6
052			
<50.	Mens.	167	26.9
	Non-Mens.	453	73.1
≥ 50	Mens	8	5.8
	Non-Mens.	130	94.2

V. SUMMARY

Overall, this reviewer agrees with the notions that no treatment effect difference between menstrually- and non-menstrually-associated migraines can be confirmed based on the post-hoc analysis. However, this reviewer was not convinced that the analysis can support the sponsor's confirmatory claim of "efficacy was unaffected by relationship to menses". The reasons can be put into the following aspects :

1. The results were post-hoc findings. The suitability of pooling the studies was not fully convincing. In general, this submission does not meet the regulatory standard for the efficacy claim.
2. The interpretation of the results was not a confirmatory one. This analysis that demonstrated no statistical significance of menses by treatment interaction does not provide the evidence of no menses association of the drug efficacy.
   The result can only be interpreted as that the relationship of the drug efficacy and the menstrual status can not be confirmed.
3. The menstrual association was strongly confounded with ages, so the menstrually-related treatment effect was not very clear due to the age confounding;
4. The power calculated based on the observed data was quite low to detect the menstrual status by treatment interaction.

/S/

Yuan-Li Shen, Dr. PH
Mathematical Statistician

Concu /S/

Dr. Jin /S/ Dr. Chi

CC:
NDA: 20-864/SE8-005
HFD-120/Dr. Katz
HFD-120/Dr. Oliva
HFD-120/Ms. Chen
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Shen

Note : This document was saved in c:\nda2000\rizatriptan\rizatriptan_stat.doc.

Reference :

1. Fleiss, J. L. (1981). Statistical methods for rates and proportions, 2nd ed. New York: Wiley.

REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG:	**Maxalt Tablets (NDA 20-864)**	**Maxalt MLT Orally Disintegrating Tablets (NDA 20-865)**
Supplements:		
(last approved)	SE8-002 (approval date 6-21-2000)	SE8-004 (approval date 6-21-2000)
Label Code: PI:	#9122104	
PPI:	#9122200	
(pending action)	SLR-004 (dated 11-11-99) SE8-005 (dated 3-10-2000) SLR-007 (dated 11-2-2000)	SLR-005 (dated 11-11-99) SE8-006 (dated 3-10-2000) SLR-007 (dated 11-2-2000)

Note of interest:

- Since Maxalt Tablets and Maxalt-MLT Orally Disintegrating Tablets share the same product labeling, this labeling review will incorporate both products.

REVIEW

20-864/SLR-004
20-865/SLR-005
Dated: 11-11-99
Amended: 11-7-2000
CBE: Yes
Label Code: PI: #9122103
PPI Code: PPI: #9122201
Reviewed by Medical Officer:

Yes Acceptable, contingent upon further revision of the WARNINGS: Cardiac Events section and the ADVERSE REACTIONS section. These comments were sent to the firm in a FAX on October 10, 2000 and were accepted in a labeling supplemental amendment dated November 7, 2000.

The supplement provides for revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the label, based on post-marketing experience in patients with risk factors predictive of CAD: myocardial ischemia or infarction, cerebrovascular accident, and dysgeusia. Additionally, the Patient Package Insert (PPI) has been updated to reflect the changes to the package insert.

20-864/SE8-005
20-865/SE8-006
Dated: 3-10-2000
Amended: 4-27-2000 (20-864/S-005 only)
7-5-2000
10-25-2000
11-7-2000
CBE: No

Label Code: N/A, draft labeling (changes to #9122105)
Reviewed by Medical Officer: Yes, recommended changes to firm's labeling proposal.
Reviewed by Pharmacologist: Yes, recommended changes to firm's labeling proposal.

The comments from both the Medical Officer and Pharmacologist were sent to the firm in a FAX on October 10, 2000 and were accepted in a labeling supplemental amendment dated 11-7-2000.

The supplement provides for 1) labeling changes regarding the relationship of menses and migraine attacks, and 2) a response to a Phase IV commitment to conduct ICH pre- and post-natal developmental toxicity study in rats using doses that produce adequate evidence of maternal toxicity.

20-864/SLR-007
20-865/SLR-007
Dated: 11-2-2000
CBE: Yes
Label Code: draft
Reviewed by Medical Officer: Yes, Acceptable

The supplement provides for a revision in the ADVERSE REACTIONS, Post-Marketing Experience section of the package insert to add the following reaction: "Skin and Skin Appendage: Toxic Epidermal Necrolysis (TEN)"

CONCLUSIONS

The supplements only provide for the labeling revisions provided for/or agreed to by the firm in their supplemental amendment dated November 7, 2000. See attached labeling which provides documentation of all changes to the package insert since original approval.

With regard to the Patient Package Insert, the attached labeling identifies all changes since original approval.

I recommend issuing an approval letter with attached draft labeling for the above supplemental applications

Robbin Nighswander, R.Ph.
Senior Regulatory Project Manager

John Purvis
Supervisory Consumer Safety Officer

Cc:
NDA 20-864
NDA 20-865
HFD-120/Div Files
HFD-120/Feeney/Oliva/Nighswander
LABELING REVIEW

35 page(s) of revised draft labeling has been redacted from this portion of the review.

Director
Regulatory Affairs

PO Box 4 BLA-20
West Point PA 19486-0004
Tel 610 397 2850
Fax 610 397 2516

MERCK

November 29. 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-007: MAXALT™ Tablets
(rizatriptan benzoate)

NDA 20-865/S-007: MAXALT-MLT™ Orally Disintegrating Tablets
(rizatriptan benzoate)

GENERAL CORRESPONDENCE

Reference is made to a Changes Being Effected Supplemental New Drug Application for proposed revisions to the Maxalt™ product labeling submitted for Agency review on November 2. 2000. Reference is also made to a telephone conversation between Mr. Robbin Nighswander, Senior Regulatory Project Manager, FDA, and Dr. Charlene G. Sanders, Merck Research Laboratories, a Division of Merck & Co., Inc. on November 28, 2000 whereby a request for a copy of the report describing the occurrence of TEN (toxic epidermal necrolysis) in a patient on Maxalt™ be submitted to accompany S-007. With this letter, we are submitting in hard copy, the requested Adverse Reaction report to facilitate agency review of this supplement.

We are simultaneously submitting this information to NDA 20-865 MAXALT-MLT™ Orally Disintegrating 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,

Dennis M. Erb (for)
Charlene G. Sanders, M.D.
Director
Regulatory Affairs

Attachment (WAES Report 00033801)

Federal Express

Desk Copy: Mr. Robbin Nighswander, HFD-120, Room 4029
(Facsimile 301-594-2859)
Ms. Lana Chen, HFD-120, Room 4031

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