# DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

# CLINICAL REVIEW OF NDA

| | |
|---|---|
| **Brand Name:** | **Maxalt RPD** |
| **Generic Name:** | **rizatriptan** |
| **Sponsor:** | **Merck** |
| **Indication:** | **migraine** |
| **NDA Number:** | **20-865** |
| **Original Receipt Date:** | **6/30/97** |
| **Clinical Reviewer:** | **Armando Oliva, MD** |
| **Review Author:** | **Armando Oliva, MD** |
| **Review Completed:** | **4/2/98** |

# *Table of Contents*

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# 1. Review Sources

The Maxalt RPD (rapidly disintegrating tablets) NDA was submitted along with the tablet NDA. The two NDA's were provided as an entirely electronic submission and it is this electronic version which I used in my review. The NDA for the RPD formulation cross-references the tablet NDA (20-864). As a result, much of the introductory and background information are the same for both applications and I refer the reader to my review of the tablet NDA for details common to both. Throughout the review, I emphasize the differences between the RPD and tablet applications, when applicable. Table 1 lists the sources used for this review.

*Table 1: Review Sources*

| Source | Submission Date | Material |
|---|---|---|
| electronic NDA | 6/30/97 | Maxalt RPD NDA in electronic format |
| electronic datasets | 6/30/97 | electronic datasets |
| updated efficacy datasets | 2/98 | electronic datasets |

# 2. Background

The RPD formulation is a novel oral formulation that dissolves instantly on the tongue. It has the practical advantage over the tablet in that no liquids are necessary for swallowing. The active agent, rizatriptan, is swallowed with the saliva and absorbed from the gastrointestinal tract.

The sponsor developed the RPD formulation with the notion that some migraine sufferers experience difficulty swallowing liquids during a migraine attack; therefore, an orally administered dosage form that does not require liquids for administration would be desirable.

## *2.1 Indication*

The proposed indication is for the treatment of acute migraine attacks with or without aura.

## *2.2 Important Information from pharmacologically related agents*

Rizatriptan is pharmacologically similar to sumatriptan. Because of the potential for this class of compounds (5-$HT_{1D/1B}$ agonists) to cause coronary vasospasm, they should not be used in patients with coronary artery disease (CAD) or in patients in whom unrecognized CAD is likely without a prior evaluation.

## *2.3 Administrative History*

This is described in the my review of the tablet NDA and is not repeated here.

## *2.4 Proposed Labeling*

The labeling of the RPD formulation is incorporated in the labeling of the tablet.

### *2.4.1 Indication*

Maxalt is indicated for the treatment of acute migraine attacks with or without aura.



### *2.4.2 Dosing*

The intended recommended initial dose is 10 mg tablet or RPD. Five mg has also been shown to be effective, but is less so. The dose may be repeated every two hours for recurrence, up to a maximum of 30 mg in a 24 hour period. Patients on propranolol should take 5 mg.

### *2.4.3 Contraindication, Warnings, and Precautions*

Maxalt is contraindicated in patients with established coronary artery disease, uncontrolled hypertension, known hypersensitivity to the formulation, or to anyone using an MAO inhibitor within two weeks.

Maxalt should not be used in patients with basilar or hemiplegic migraine, nor in patients without a clear diagnosis of migraine. Other $5HT_{1D}$ agonists should not be used with Maxalt. Ergotamine type medications (*e.g.*, ergotamine tartrate, DHE) should not be given within 6 hours of Maxalt use.

Rare reports of serious coronary events with another drug in this class have been reported. Prior to the use of this drug, a cardiovascular assessment should be considered in patients with know risk factors for coronary artery disease.

Phenylketonurics should be aware that RPD contains phenylalanine.

Maxalt may cause drowsiness in some patients.



### *2.4.4 Drug Interactions*

MAO-A inhibitors can cause significant elevations in Maxalt serum concentrations (up to 400%). The use of MAO inhibitors in this setting is contraindicated.

Propranolol 240 mg/day caused a 70% increase in Maxalt serum concentrations.

### *2.4.5 Carcinogenesis, Mutagenesis, Fertility*

No evidence of carcinogenicity, genotoxicity, mutagenicity, clastogenicity was seen. No adverse effects on fertility, reproductive performance, and no fetal toxicity was seen in rats and rabbits. Pregnancy: Category B.

### *2.4.6 Special Populations*

Nursing Mothers: no data exist in human. Rizatriptan is excreted in rat milk with a very high transfer rate, with milk levels exceeding plasma levels by 5 fold or more.

Safety and efficacy in pediatric patients have not been established.

The PK of rizatriptan was similar in elderly and young adults. Experience in the elderly is limited (n=17 over age 65) but there were no apparent differences in efficacy or safety in this population.

### *2.4.7 Adverse Events*

Maxalt was generally well tolerated. Most common AE's were dizziness (8%), somnolence (8%), asthenia/fatigue (5%), nausea (4%), chest pain (3%) , and paresthesias (3%). No serious adverse events were reported.

### *2.4.8 Drug Abuse and Dependence*

None seen.

### *2.4.9 Overdose*

None seen. In a clinical pharmacology study, 12 subjects received a cumulative dose of 80 mg over 4 hours. Two subjects experienced syncope and/or bradycardia (including 3$^{rd}$ degree AV block treated with atropine and a 5 second systolic pause after a painful venipuncture).

### *2.5 Foreign Marketing*

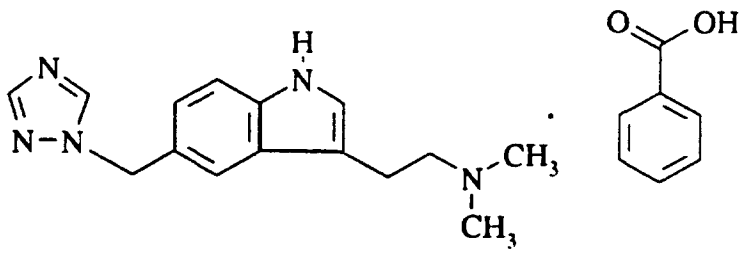
Rizatriptan has not been marketed in any country. As of the NDA submission date, 6/30/97, there were no pending applications in any other country.

## 3. Chemistry, Manufacturing and Controls

Rizatriptan benzoate is a white to off-white powder. Five (5) mg and 10 mg tablets have been developed, as well as 5mg and 10mg rapidly disintegrating tablet (RPD) formulations.

| | |
|---|---|
| **Generic Name:** | **rizatriptan benzoate** |
| **Trade Name:** | **Maxalt™** |
| **Chemical Name:** | ***N,N*-Dimethyl-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1*H*-indole-3-ethamine monobenzoate** |
| **Alternative Name:** | **MK-0462** |
| **Molecular Formula:** | **$C_{15}H_{19}N_5 \bullet C_7H_6O_2$** |
| **Molecular Weight:** | **391.47** |

*Figure 1: Rizatriptan, chemical structure*



According to the review chemist, Dr. Bates, both 5 and 10 mg discs have remained stable up to 18 months real time.

## 4. Animal Pharmacology & Toxicology

Rizatriptan is a $5HT_{1B/1D}$ agonist. I refer the reader to the Maxalt tablet NDA review for additional animal pharmacology and toxicology information about this compound. Dr. Tom Steele, the pharm/tox reviewer, agrees with Dr. Bates that the sponsor qualified the degradate at a level of 2% in several toxicology studies so no additional toxicology testing is necessary.

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## 5. Clinical Data Sources

### *5.1 Study Type*

The sponsor uses the data sources already reviewed in the Maxalt tablet NDA as supportive for the RPD formulation. In addition, there are three studies specific to the RPD formulation. These are shown in Table 2.

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*Table 2: Summary of Maxalt RPD Clinical Program*

| Study | Title |
|---|---|
| *Phase 1* | |
| 033 | Open Study of the PK, Safety, and Tolerability of Maxalt RPD 10mg and Tablets |
| 042 | Open Bioavailability Study of Maxalt RPD 5mg and 10mg and Tablets |
| *Phase 3* | |
| 039 | Double-blind Study of the Efficacy and Safety of Maxalt RPD 5mg and 10mg for the Acute Treatment of Migraine |

### *5.2 Demographics*

The demographic characteristics of the subjects exposed in phase 1 studies 033 and 042 are shown in Table 3.

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*Table 3: Studies 033, 042 - Baseline Demographic Characteristics*

| Demographic Characteristics | Rizatriptan 5 mg RPD (N=12) | Rizatriptan 10 mg RPD (N=36) |
|---|---|---|
| *Gender:* | | |
| Male | 0 | 24 |
| Female | 12 | 12 |

| Demographic Characteristics | Rizatriptan 5 mg RPD (N=12) | Rizatriptan 10 mg RPD (N=36) |
|---|---|---|
| *Age (Years):* | | |
| 18 to 29 | 9 | 26 |
| 30 to 39 | 3 | 8 |
| 40 to 49 | 0 | 2 |
| Mean | 27 | 27 |
| Median | 28 | 26 |
| Range | | |
| *Origin:* | | |
| White | 12 | 26 |
| Black | 0 | 8 |
| Hispanic | 0 | 0 |
| Asian | 0 | 2 |
| Other | 0 | 0 |
| Unknown | 0 | 0 |

The majority of the subjects were white. The percentage of blacks treated (33%) was considerably higher than in the phase 3 studies of both RPD and tablet (<5%) but the absolute numbers were small. The population was also younger than the phase 3 population and had more men on a percent basis.

The demographics for the large efficacy study 039 are shown in Table 4.

*Table 4: Study 039 - Baseline Patient Demographics*

| Demographic Characteristics | Rizatriptan 5 mg RPD (N= 100) | Rizatriptan 10 mg RPD (N= 114) | Placebo (N= 98) | Total (N= 312) |
|---|---|---|---|---|
| *Gender:* | | | | |
| Female | 89 (89%) | 102 (89%) | 83 (85%) | 274 (88%) |
| Male | 11 (11%) | 12 (11%) | 15 (15%) | 38 (12%) |
| *Age (Years):* | | | | |
| 18 to 29 | 15 (15%) | 23 (20%) | 17 (17%) | 55 (18%) |
| 30 to 39 | 39 (39%) | 38 (33%) | 25 (26%) | 102 (33%) |
| 40 to 49 | 27 (27%) | 33 (29%) | 32 (33%) | 92 (29%) |
| 50 to 59 | 17 (17%) | 15 (13%) | 20 (20%) | 52 (17%) |
| 60 to 64 | 2 (2%) | 4 (4%) | 3 (3%) | 9 (3%) |
| >64 | 0 | 1 (1%) | 1 (1%) | 2 (1%) |
| Mean | 39.4 | 39 | 41.3 | 39.8 |
| SD | 9.9 | 10.7 | 10.7 | 10.5 |
| Median | 38 | 39 | 41.5 | 39 |
| Range | | | | |
| *Racial Origin:* | | | | |
| White | 92 (92%) | 107 (94%) | 85 (87%) | 284 (91%) |
| Black | 5 (5%) | 2 (2%) | 9 (9%) | 16 (5%) |
| Asian | 1 (1%) | 1 (1%) | 0 | 2 (1%) |
| Hispanic | 2 (2%) | 4 (4%) | 4 (4%) | 10 (3%) |
| *Baseline Severity:* | | | | |
| Moderate | 63 (63%) | 69 (60.5%) | 67 (68.4%) | 199 (63.8%) |
| Severe | 37 (37%) | 44 (38.6%) | 31 (31.6%) | 112 (35.9%) |
| Missing | 0 | 1 (0.9%) | 0 | 1 (0.3%) |
| *Presence of Aura:* | | | | |

| Demographic Characteristics | Rizatriptan 5 mg RPD (N= 100) | Rizatriptan 10 mg RPD (N= 114) | Placebo (N= 98) | Total (N= 312) |
|---|---|---|---|---|
| With | 8 (8.0%) | 17 (14.9%) | 11 (11.2%) | 36 (11.5%) |
| Without | 92 (92.0%) | 97 (85.1%) | 87 (88.8%) | 276 (88.5%) |
| *Prophylactic Treatment:* | | | | |
| With Any | 3 (3.0%) | 2 (1.8%) | 2 (2.0%) | 7 (2.2%) |
| Beta Blockers | 0 | 0 | 1 (1.0%) | 1 (0.3%) |
| Calcium Channel Blockers | 1 (1.0%) | 2 (1.8%) | 0 | 3 (1.0%) |
| Tricyclic Antidepressants | 1 (1.0%) | 0 | 0 | 1 (0.3%) |
| Valproate | 1 (1.0%) | 0 | 1 (1.0%) | 2 (0.6%) |
| Without | 97 (97.0%) | 111 (97.4%) | 96 (98.0%) | 304 (97.4%) |
| Missing (lost to follow-up) | 0 | 1 (0.9%) | 0 | 1 (0.3%) |
| *Oral Contraceptives in Women* | | | | |
| With | 11 (12.4%) | 24 (23.5%) | 11 (13.3%) | 46 (16.8%) |
| Without | 78 (87.6%) | 77 (75.5%) | 72 (86.7%) | 227 (82.8%) |
| Missing (lost to follow- up) | 0 | 1 (1%) | 0 | 1 (0.4%) |

As in the tablet studies, the majority were female (88%) and white (91%) and averaged 40 years of age ). Roughly two-thirds treated a moderate headache and one-third treated a severe headache. Approximately 2% were taking concomitant prophylaxis medication.

### *5.2.1 Extent of Exposures*

There were 250 patients who received rizatriptan RPD in the three RPD studies. Of these, 214 were exposed in the phase 3 study 039 and 36 were exposed in the two phase 1 studies 033 and 042. Twenty-four (24) subjects in the two phase 1 trials also received rizatriptan tablets.

Study 033 enrolled 12 normal healthy male volunteers and study 042 enrolled 24 healthy subjects (12 males and 12 females). The two phase 1 studies were crossover studies by design; therefore, 12 subjects received 5mg for one day, 36 received 10mg for one day, and 12 of these received both 5mg and 10mg for one day each.

In study 039, a total of 100 patients treated one attack with 5mg, 114 patients treated one attack with 10mg, and 98 took placebo. Patients could take up to 3 doses in a 24 hour period. The majority took only one dose of rizatriptan. This is shown in Table 5.

***Table 5: Study 039 - Number of Patients by Dosage, and Number of Doses Taken***

| Rizatriptan RPD | | | | | | | | PBO | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 mg | | | | 10 mg | | | | (N Doses Per Attack) | | | |
| 1 | 2 | 3 | Total | 1 | 2 | 3 | Total | 1 | 2 | 3 | Total |
| 58 | 27 | 15 | 100 | 81 | 23 | 10 | 114 | 64 | 26 | 8 | 98 |

This shows that for the 5mg RPD, 27% took 2 doses and 15% took 3 doses. For the 10mg RPD, 20% took two doses, and 9% took three doses. These are

similar to the tablet experience, where 25% took 2 doses and 11% took 3 doses for the 5mg and 10mg tablets.

### *5.3 Adequacy of Human Experience*

In light of the large and extensive experience with rizatriptan in the tablet NDA, the additional experience with the RPD formulation, when taken in combination, provides a robust human experience with the drug, in my opinion.

The use of the tablet experience to support approval of the RPD formulation is valid, in my opinion, since the tablet and RPD are administered orally, and the PK and metabolism of the two formulations are similar (see below).

## 6. Human Pharmacokinetics

The PK program of the RPD wafer was conducted primarily in healthy adult subjects . The sponsor uses information gathered from the tablet PK studies as supportive for the RPD wafer. I don't include this information here but refer the reader to the clinical and biopharmaceutical review of the tablet NDA. I include here PK information pertinent to the RPD.

Two PK studies were conducted with the RPD formulation: a relative bioavailability study in male subjects (study 033) and a final market image bioavailability study in male and female subjects (study 042). Key PK parameters for the RPD wafer are shown below, with comparison with tablet.

*Table 6: Pharmacokinetics of RPD Formulation*

| Parameter | RPD | Tablet |
|---|---|---|
| $C_{max}$ (5mg) | ~10 ng/mL | ~10 ng/mL |
| $C_{max}$ (10mg) | ~20 ng/mL | ~20 ng/mL |
| $T_{max}$ | 1.5-2.5 hours | 1-1.5 hours |
| $T_{1/2}$ | 2-3 hrs | 2-3 hrs |



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The time to maximum plasma concentration ($T_{max}$) is delayed for RPD relative to tablet by 30-60 minutes, otherwise the PK is very similar between the two formulations.

Plasma concentrations and urinary excretion of N-monodesmethyl-rizatriptan (which is twice as active as the parent) following RPD administration are the same as following tablet administration. The metabolite-to-parent ratio for AUC averages following administration of either dosage form.

## 7. Integrated Review of Efficacy

### *7.1 Study 039*

The sponsor submitted one study, 039, to support the efficacy of Maxalt PRD for the treatment of migraine. It was a randomized, double-blind, placebo controlled, parallel groups, outpatient study which examined the efficacy and safety of

Maxalt RPD 5mg and 10mg for the acute treatment of migraine. A more detailed description of the protocol is provided in Appendix A, page 47. Patients were instructed to treat a grade 2 or 3 headache with study medication. Remedication for up to two recurrence within 24 hours was permitted with the same blinded dose of study medication used for the initial attack, with a maximum permitted dose within 24 hours of 30mg. Rescue was allowed after 2 hours of treatment of an initial attack or recurrence.

The primary analysis compared the two hour headache response, measured in the traditional manner using a 4 point headache scale (0-3 for none, mild, moderate, severe). A two hour responder was defined as a patient with a grade 2 or 3 headache at baseline and a grade 0 or 1 headache at 2 hours.

Secondary endpoints included the complete headache relief rate at 2 hours, absence of associated symptoms at 2 hours (nausea, vomiting, photophobia, phonophobia), absence of functional disability at 2 hours, and need for rescue after initial dose.

Additional secondary endpoints included the rates of taste acceptability, and formulation preference (between RPD and tablet).

### *7.2 Results - Sponsor's Analysis*



#### *7.2.1 Sample Size*

With a planned sample size of 80 patients per treatment arm (5mg, 10mg, placebo), the study had >95% power to detect a 30 percentage point difference (50% vs. 20%) based on a two-sided test using an $\alpha$=0.05.

#### *7.2.2 Disposition*

A total of 381 patients entered the study. Sixty-nine (69) patients who were randomized did not take study medication and were excluded from any subsequent tabulations and analyses. Among the remaining 312 patients who took study medication, 100 were in the rizatriptan 5mg group, 114 took 10mg, and 98 took placebo. All results are based on these 312 patients. A summary of patient disposition is shown in Table 7.

***Table 7: Study 039 - Patient Disposition***

| | Riza 5 mg | Riza 10mg | Placebo | Total |
|---|---|---|---|---|
| *Patients Randomized* | *126* | *127* | *128* | *381* |
| *Patients Treated* | *100* | *114* | *98* | *312* |
| *Patients Not Treated* | *26* | *13* | *30* | *69* |
| Patients Treated | | | | |
| Completed Study | 100 | 113 | 97 | 310 |
| Clinical AE Dropout | 0 | 0 | 0 | 0 |
| Lost to Follow-up | 0 | 1 | 0 | 1 |
| Deviation From Protocol | 0 | 0 | 0 | 0 |
| Withdrew From Study | 0 | 0 | 0 | 0 |
| Patient Uncooperative | 0 | 0 | 1 | 1 |

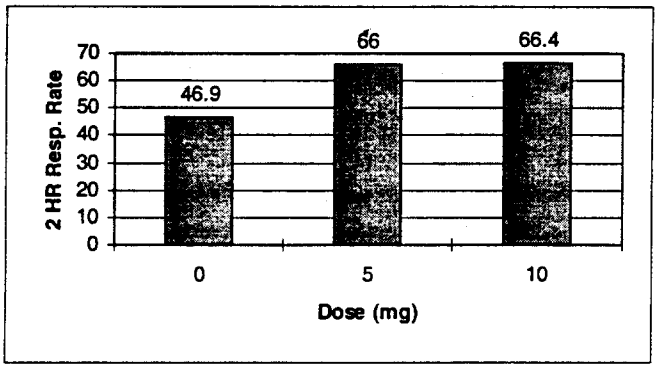
| | Riza 5 mg | Riza 10mg | Placebo | Total |
|---|---|---|---|---|
| Patients Not Treated | | | | |
| Lost to Follow-up | 4 | 3 | 7 | 14 |
| Withdrew from Study | 4 | 0 | 0 | 4 |
| Abnormal Prestudy Labs | 1 | 0 | 3 | 4 |
| Abnormal baseline ECG | 1 | 0 | 0 | 1 |
| Need for Concom. Med. | 0 | 0 | 1 | 1 |
| Lack of Migraine Attack | 14 | 8 | 16 | 38 |
| Other | 2 | 2 | 3 | 7 |

## *7.2.3 Efficacy Parameters*

As in the migraine efficacy studies for the tablet, the primary efficacy parameter measured the two hour headache response rate in all three groups, as previously defined.

At two hours, the percentages of patients reporting pain relief were 66.0%, 66.4%, and 46.9% for 5mg, 10mg, and placebo, respectively (Figure 2).

***Figure 2: Study 039 - Two Hour Headache Response Rate***




Other efficacy results are shown in Table 8.

***Table 8: Study 039, Efficacy Measures for RPD***

| Measure | Rizatriptan 5 mg n=100 | Rizatriptan 10 mg n=113 | Placebo n=98 |
|---|---|---|---|
| Headache-Related Measures | | | |
| Pain response 2 Hrs | 66.0* | 66.4* | 46.9 |
| Pain-free 2 Hrs | 33.0** | 37.2* | 17.3 |
| Escape medication | 29.0** | 28.3** | 44.9 |
| Recurrence (within 24 hr)[1] | 41.9 | 33.7 | 35.8 |
| Associated Symptoms | | | |
| Nausea | 23 | 25.7 | 33.7 |
| Vomiting | 5.0 | 5.3 | 5.1 |
| Photophobia | 43.0* | 41.6* | 64.3 |
| Phonophobia | 32.0** | 36.3** | 51.0 |
| Other Measures | | | |
| % No Functional Disability | 41.0** | 43.4** | 31.6 |
| Acceptable Taste | 87.0 | 79.6 | 94.9 |
| Prefer RPD over Tablet | 63.0 | 56.6 | 63.3 |

* p<0.01 compared to placebo
** p<0.05 compared to placebo

[1] defined as return of grade 2 or 3 pain within 24 hours after initial treatment in a patient who achieved a response at 2-4 hours

Both doses of RPD were better than placebo ($p \leq 0.007$). There was no difference between the two rizatriptan doses ($p=0.980$). There was no significant effect of treatment site on efficacy. Although patients with moderate baseline severity had higher headache response rates than those with severe headaches at baseline, the difference was not statistically significant ($p=0.161$).

There were no significant effects on efficacy due to gender, age, group, aura, use of migraine prophylaxis, and use of contraceptives in females. Race (white vs. other) did had a notable effect on efficacy. The two hour response rate was higher in non-white patients than in the white patients (75% vs. 65% for 5mg, and 86% vs. 65% for 10mg). However, the numbers of non-whites in the study were very small (n=6 for each active treatment group) and these results should be interpreted with caution.

With regard to secondary variables, pain-free rates at 2 hours were statistically better for both 5mg and 10mg compared to placebo. The need for escape medication was significantly less for patients treated with either active dose. The only other measures where treatment appeared to have an advantage were in photophobia, phonophobia and functional disability at 2 hours.

The sponsor also measured headache response rates at 0.5, 1, 1.5, 3, and 4 hours. The results for 0-2 hours (prior to remedication) are shown in Table 9 (adapted from ISE Table D-40, page D-131). The same data are shown graphically in

*Table 9: Study 039, Response Rates at Various Time-Points* (%)*

| *Time (hrs)* | *0.5* | *1* | *1.5* | *2* | *3* | *4* |
|---|---|---|---|---|---|---|
| PBO | 16.3 | 30.6 | 40.8 | 46.9 | 58.2 | 65.3 |
| 5mg RPD | 18 | 40 | 58 | 66 | 72 | 83 |
| 10mg RPD | 17.7 | 43.4 | 56.6 | 66.4 | 75.2 | 79.6 |

*Remedication permitted after 2 hours

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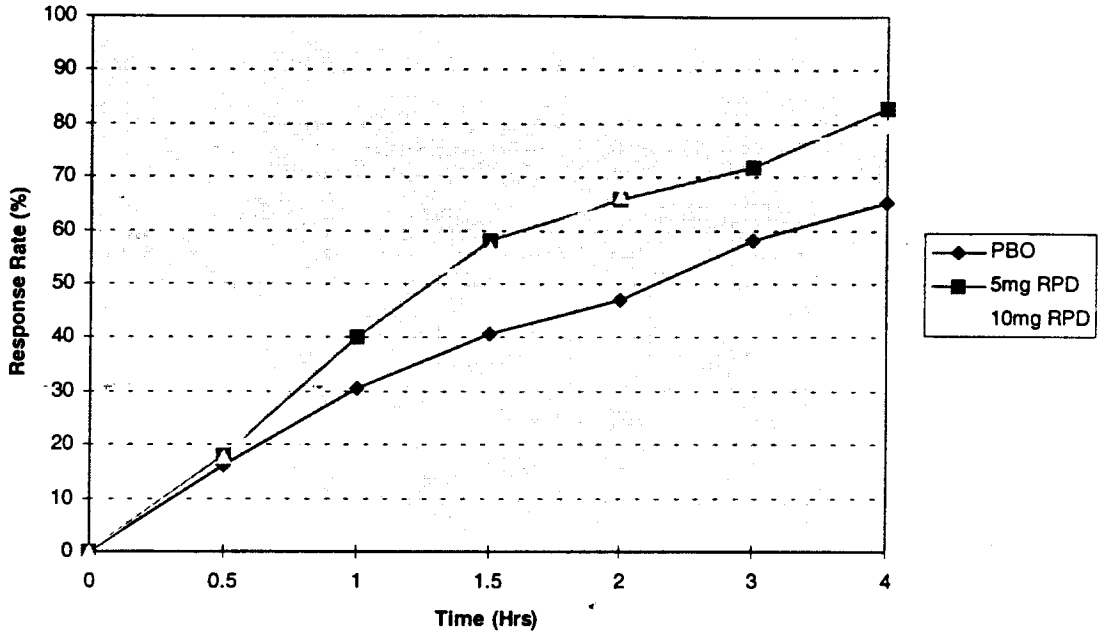
*Figure 3: Study 039 - Response Rates over Time (1-4 Hours)*




Both doses of 5mg and 10mg were better than placebo starting at 1.5 hours. There was a numerical advantage to the drug at 1 hour but it did not achieve statistical significance.

### *7.2.4 Sponsor's Conclusions*

1. Both doses of rizatriptan RPD (5mg and 10mg) provide relief from moderate and severe migraine headache beginning 1 hour after dosing[1].
2. Both doses of rizatriptan RPD are effective in producing complete relief and in reducing functional disability and associated migraine symptoms of photophobia and phonophobia, as well as reducing the need for additional analgesic/antiemetic medications.

## *7.3 Reviewer's Analyses*



### *7.3.1.1 Methods and Demographic Considerations*

I used the efficacy dataset provided by the sponsor to perform my own analyses. In all cases, I used JMP version 3.2.2. I analyzed the 2 hour response rates for each treatment group. I did not repeat the secondary efficacy analyses.

There were 311 patients in the efficacy dataset. All 311 treated the first attack, 108 took a second dose, and 33 took a third dose. My analyses focused on treatment of the initial attack. The mean age of the population was 39.9. Two hundred seventy-three (273), or 88%, were female, and the population was predominantly white (283 or 91%). There were 16 blacks in the study. The study population demographics, by treatment group, is shown in Table 10.

[1] The numbers at 1 hour were not statistically significant.

*Table 10: Study 029 - Demographics*

| | PBO (n=98) | Rizatriptan 5mg (n=100) | Rizatriptan 10mg (n=113) |
|---|---|---|---|
| Mean Age | 38.3 | 38.3 | 37.0 |
| Females | 83 (85%) | 89 (89%) | 101 (89%) |
| White | 85 (87%) | 92 (92%) | 106 (94%) |
| Baseline Severity = 2 | 67 (68%) | 63 (63%) | 69 (61%) |

The three treatment groups were very similar to each other with respect to mean age, gender, race, and baseline severity.

### *7.3.1.2 Primary Efficacy - 2 Hour Response Rates*

Of the 311 patients who treated the first attack, all recorded a baseline headache score and all recorded either a grade 2 or 3 headache at baseline. Ninety-eight (98) took placebo, 100 took rizatriptan 5mg, and 113 took rizatriptan 10mg. Of these 311 patients, all patients recorded at least one post-treatment headache score. Five (5) patients did not record a 2 hours headache score, but I was able to impute missing values using an LOCF approach.

Sixty-six percent (66%) of the rizatriptan 5 mg group achieved a response at 2 hours, compared to 66.4% for rizatriptan 10mg, and 47% for placebo (FDA Table 11). Both doses were better than placebo ($p<0.001$ for either comparison, Fisher's Exact Test).

*Table 11: Study 039 - Two Hour Response Rate (Reviewer's Analysis)*

| Treatment | Response | No Response |
|---|---|---|
| PBO (n=98) | 46 (47%) | 52 (53%) |
| Rizatriptan 5mg (n=100) | 66 (66%) | 34 (34%) |
| Rizatriptan 10mg (n=113) | 75 (66.4%) | 38 (33.4%) |

p=0.0056 (Chi Square Test) for overall analysis

There was no difference between the two active doses ($p=1.00$, Fisher's Exact Test). I did not repeat the secondary analyses. There was a numerical advantage to 10mg over 5mg with respect to recurrence and complete relief at 2 hours, but these was not statistically significant.

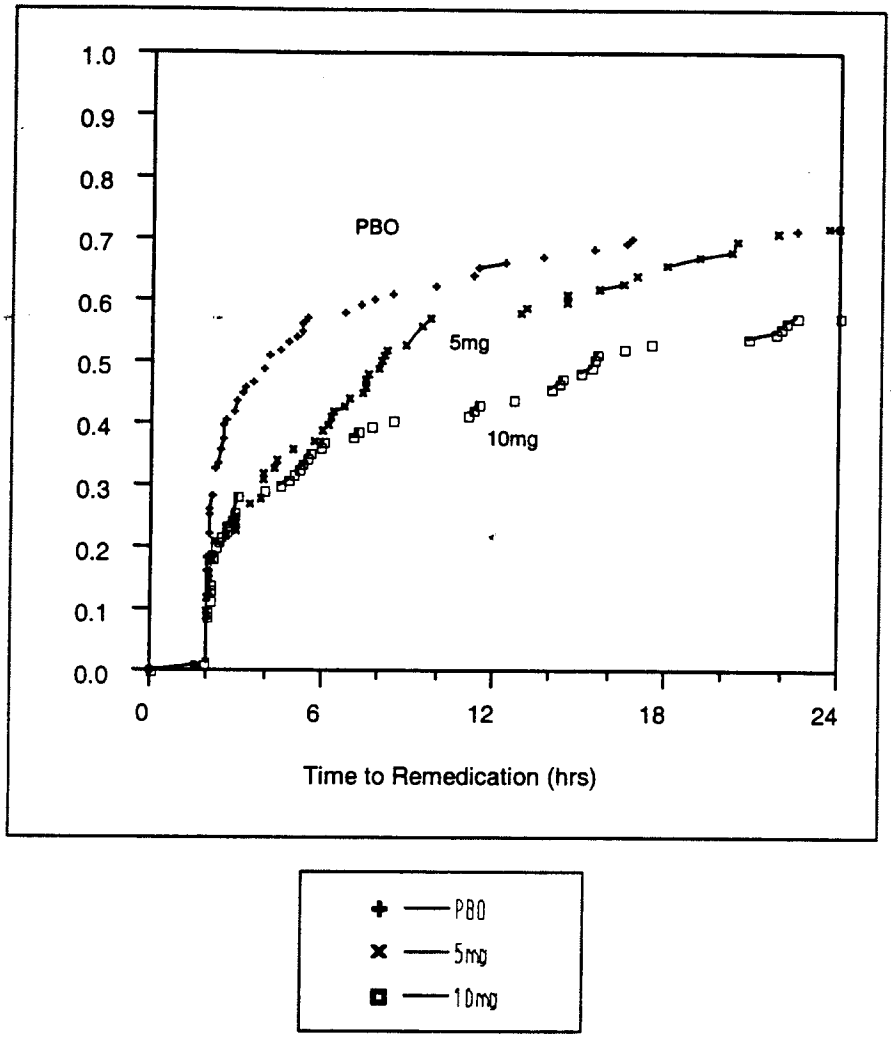
### *7.3.1.3 Time To Remedication*

Remedication was defined as any escape medication or study medication taken within the first 24 hours after the initial dose. Patients who took no additional medication within the first 24 hours after treatment were censored to 24 hours. I used the corrected efficacy dataset provided in March 1998 for the analysis.

I plotted the probability of not requiring remedication using product-limit survival estimates (Kaplan-Meier method) using JMP version 3.2.2. The graph is shown in Figure 4. It shows that patients taking 10mg had the lowest probability over time of requiring remedication. Placebo patients had the highest. Patients were

not allowed to remedicate prior to 2 hours, which explains why the curve is practically flat between 0-2 hours.

***Figure 4: Study 039 - Probability of Remedication Within 24 Hours***






## *7.3.2 Reviewer's Conclusions*

1. Rizatriptan 5mg and 10mg RPD are both effective for the acute treatment of migraine headache.
2. Rizatriptan 5mg and 10mg RPD appeared to decrease the incidence of photophobia and phonophobia. It also decreased the need for remedication, compared to placebo, within the first 24 hours.
3. There is no statistical evidence that 10mg is any better than 5mg, although the 10mg was numerically better in certain secondary outcome measures (*e.g.*, complete relief at 2 hours, recurrence).

# 8. Integrated Review of Safety

## *8.1 Background and Methodology*

The systemic effects of Maxalt RPD were monitored in the same fashion as they were in the tablet development programs. Safety data collected included spontaneous adverse event reports, physical examination, vital signs, laboratory data, and 12-lead ECG. Clinically significant changes in these parameters were reported by investigators as adverse experiences.

Master line listings and patient narratives were provided for each patient who discontinued due to an adverse event, experienced a serious adverse event, exhibited potentially clinically significant laboratory, vital sign, or ECG abnormality.

## *8.2 Deaths*

There were no deaths reported.



## *8.3 Serious Adverse Events*

There were two serious adverse events reported among all clinical studies involving the RPD formulation. One was an elective abortion and the second was a spontaneous abortion. I briefly mentioned the spontaneous abortion report in the tablet NDA review and I review it here in more detail. Since the elective abortion was just that, elective, I don't discuss it here.

A **44 y/o female** (039-010 0255) entered the study on 2/29/96 and was randomized to receive RPD 5mg. On 3/19/96, she took one dose of rizatriptan RPD 5mg for a migraine and she returned the remaining doses to the investigator at the post-treatment visit on 3/22/96. Concomitant therapy included butalbital-caffeine-acetaminophen (ESGIC), sumatriptan succinate (Imitrex) and duradrin. On 4/4/96 she called the clinic to report that she suspected she might be pregnant because of an estimated last menstrual period of 3/1/96. She returned to the clinic on 4/8/96 and a serum HCG was positive. On 4/30/96 she called the clinic and reported that she had experienced vaginal bleeding and cramping 4/22/96-4/26/96. She experienced a spontaneous miscarriage on 4/26/96 and she underwent a routine D&C. The investigator felt the spontaneous abortion was unrelated to study medication.

In my opinion, it is unlikely the study medication caused the abortion as the event occurred over one month from ingestion of a single dose of rizatriptan RPD 5mg.

## *8.4 Dropouts and "Other Significant Adverse Events"*

### *8.4.1 Dropouts*

In the phase 1 studies, no patients on RPD discontinued. Two of 38 patients discontinued due to clinical adverse experiences following a single 10mg dose of tablet. These were included in the review of the tablet NDA and are not discussed here.

According to case report forms received from study 039 as of 9/27/96, no patient discontinued therapy due to a clinical adverse experience following a dose of rizatriptan RPD. This is not entirely surprising given the single dose study design

and the relatively small number of patients exposed to RPD compared to the tablet experience.

### *8.4.2 Other Significant Adverse Events*

No other significant adverse events were reported.



## *8.5 Adverse Events Incidence Tables*

### *8.5.1 Phase 1*

Of the 36 healthy subjects who received rizatriptan 5mg and/or 10mg, there were 6 subjects who had one or more AE (17%). The only AE occurring in more than one subject was headache, which occurred in 2 of 36 (one subject on 5mg and one subject on 10mg). A complete listing of all AE's experienced by these six subjects is shown in sponsor Table 12 (ISS Table D-139, page D-457).

*Table 12: Adverse Events Reported in Phase 1 Maxalt RPD Studies, (%)*

| | RPD 5 mg (N= 12) | | RPD 10mg (N= 36) | | Rizatriptan Tablets (N= 26) | | Any Formulation (N= 38) | |
|---|---|---|---|---|---|---|---|---|
| Any AE | 3 | (25) | 3 | (8) | 9 | (35) | 12 | (32) |
| Headache | 1 | (8) | 1 | (3) | 2 | (8) | 4 | (11) |
| Vasovagal reaction | 0 | | 1 | (3) | 2 | (8) | 3 | (8) |
| Diarrhea | 1 | (8) | 0 | | 2 | (8) | 2 | (5) |
| Depression | 1 | (8) | 0 | | 1 | (4) | 2 | (5) |
| Pharyngitis | 1 | (8) | 0 | | 0 | | 1 | (3) |
| Asthenia/ fatigue | 1 | (8) | 0 | | 0 | | 1 | (3) |
| Taste Perversion | 0 | | 1 | (3) | 0 | | 1 | (3) |
| Ecchymosis | 0 | | 1 | (3) | 0 | | 1 | (3) |
| Lethargy | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Burning face | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Peripheral neuropathy | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Nausea | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Chest pain | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Ear pain | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Pregnancy | 0 | | 0 | | 1 | (4) | 1 | (3) |
| Abortion | 0 | | 0 | | 1 | (4) | 1 | (3) |



### *8.5.2 Phase 3*

One or more clinical AE occurred in 44 (44%) of the 100 patients who received RPD 5mg, 52 (46%) of those who received RPD 10mg, and 34 (35%) of those who received placebo.

Nausea, dizziness, and dry mouth were the most common (≥5%) AE's seen in patients on RPD 5mg or 10mg. Nausea was present in 7%, 13%, and 8% of patients on 5mg, 10mg, and placebo, respectively. Dizziness was observed in 9%, 13%, and 7%, respectively. Dry mouth was seen in 12%, 7%, and 2%, respectively. Both nausea and dizziness were more common at 10mg than at 5mg, again suggesting a dose-response relationship. The incidence of nausea at

5mg was similar to placebo in this study. Most reports of dizziness and dry mouth were mild, whereas nausea reports were of mild to moderate in intensity.

Table 13 (adapted from ISS Table D-141, page D-464) lists the incidence of all clinical AE's in Study 039 with incidence ≥1% by treatment group and number of doses taken. The AE's reported are all similar to those reported for the tablet.

*Table 13: Study 039 - Clinical AE's in >1 Patient by Treatment Group and Number of Doses Taken, Percent Reporting*

| Number of Doses = | RPD 5mg | | | | RPD 10mg | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 (n=58) | 2 (n=27) | 3 (n=15) | Any (n=100) | 1 (n=81) | 2 (n=23) | 3 (n=10) | Any (n=114) | 1 (n=64) | 2 (n=26) | 3 (n=8) | Any (n=98) |
| % Any AE | 48 | 44 | 47 | 47 | 46 | 52 | 30 | 46 | 34 | 54 | 38 | 40 |
| Dizziness | 7 | 11 | 27 | 11 | 15 | 9 | 10 | 13 | 0 | 12 | 0 | 0 |
| Nausea | 3 | 8 | 20 | 8 | 12 | 22 | 0 | 13 | 0 | 9 | 0 | 8 |
| Dry Mouth | 14 | 11 | 13 | 13 | 5 | 17 | 20 | 9 | 2 | 4 | 13 | 3 |
| Paresthesia | 3 | 7 | 0 | 4 | 4 | 13 | 0 | 5 | 0 | 4 | 0 | 1 |
| Somnolence | 5 | 7 | 0 | 5 | 4 | 9 | 0 | 4 | 5 | 15 | 0 | 7 |
| Vomiting | 2 | 0 | 0 | 1 | 4 | 4 | 0 | 4 | 0 | 4 | 0 | 1 |
| Headache | 2 | 0 | 7 | 2 | 4 | 0 | 0 | 3 | 2 | 0 | 0 | 1 |
| Discomfort, pharyngeal | 3 | 0 | 0 | 2 | 4 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| Dyspepsia | 2 | 0 | 0 | 1 | 4 | 0 | 0 | 3 | 3 | 0 | 0 | 2 |
| Increased salivation | 0 | 0 | 0 | 0 | 3 | 4 | 0 | 3 | 0 | 0 | 0 | 0 |
| Heaviness, regional | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Palpitation | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 2 | 2 | 0 | 0 | 1 |
| Vertigo | 3 | 4 | 7 | 4 | 3 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Rhinorrhea | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Blurred vision | 2 | 0 | 0 | 1 | 3 | 4 | 0 | 3 | 0 | 0 | 0 | 0 |
| Asthenia/ fatigue | 3 | 7 | 0 | 4 | 1 | 0 | 1 | 2 | 0 | 4 | 0 | 1 |
| Pain, Chest | 3 | 0 | 0 | 2 | 1 | 4 | 0 | 2 | 2 | 0 | 0 | 1 |
| Diarrhea | 2 | 0 | 0 | 1 | 1 | 4 | 0 | 2 | 2 | 4 | 0 | 2 |
| Hypesthesia | 0 | 0 | 0 | 0 | 1 | 4 | 0 | 2 | 0 | 0 | 0 | 0 |
| Nervousness | 0 | 4 | 0 | 1 | 0 | 9 | 0 | 2 | 0 | 4 | 0 | 1 |
| Flushing | 0 | 4 | 0 | 1 | 0 | 9 | 0 | 2 | 2 | 0 | 0 | 1 |
| Sweating | 3 | 0 | 0 | 2 | 1 | 4 | 0 | 2 | 2 | 0 | 0 | 1 |
| Perversion, taste | 0 | 4 | 0 | 1 | 0 | 9 | 0 | 2 | 3 | 0 | 0 | 2 |
| Pain, abdominal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 2 |
| Tightness, regional | 2 | 0 | 7 | 2 | 0 | 4 | 0 | 1 | 2 | 0 | 0 | 1 |
| Tachycardia | 2 | 4 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 8 | 0 | 3 |
| Flatulence | 0 | 0 | 7 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 2 |
| Pain, neck | 2 | 0 | 7 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain, shoulder | 0 | 0 | 7 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 13 | 1 |
| Mental acuity decreased | 2 | 4 | 7 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tremor | 2 | 7 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 1 |
| Hot flashes | 2 | 4 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### *8.6 Laboratory Findings*

Laboratory safety measurements (hematology, chemistry, urinalysis) were performed in the phase 1 studies at pre-study, immediately before each dose of test drug, and at post-treatment. In the phase 3 study, the same lab tests were performed at the pre-study and post-treatment visits. Lab tests were analyzed locally in the phase 1 studies and at the same central lab used in the U.S. phase 3 tablet studies.

#### *8.6.1 Clinical Laboratory Adverse Events*

Laboratory data were reported as "clinical laboratory adverse experiences" (LAE) which were based on the clinical judgment of the investigator. Thus a clinically significant laboratory abnormality could be classified as an LAE by one investigator but not another. Clinical monitors reviewed all laboratory values outside the normal range to ensure that all important abnormalities were classified as LAE's by the investigators.

No subjects in the phase 1 studies had an LAE. In the phase 3 study, 039, there were six patients with LAE's, three on placebo, two on RPD 10mg, and 1 on RPD 5mg.

The three patients treated with rizatriptan RPD had the following abnormalities:

039-009-0221: ↑ bilirubin (day 6, 5mg, 21 y/o F)
039-009-0218: ↑ ALT/AST (day 7, 10mg, 30 y/o F)
039-011-0335: ↓ Hb, Hct, ↑ plats (day 3, 30mg, 43 y/o F)

The three patients on placebo RPD had the following abnormalities:

039-006-0158: ↓ glucose (day 8, 1 dose, 24 y/o F)
039-009-0238: proteinuria (day 21, 1 dose, 49 y/o M)
039-009-0226: ↑ alkaline phosphatase (day 7, 1 dose, 51 y/o F)

All abnormalities except those reported for patients 0335 and 0158 were felt to be drug related by the investigators. None was symptomatic nor serious and none resulted in discontinuation . A brief description of each LAE follows:

RPD 5mg (0221) - 21 y/o F had a total serum bilirubin of , at the post-treatment visit day 6. A repeat test 27 days later was normal This was considered possibly related to drug. There were no clinical correlates.

RPD 10mg (0218) - 30 y/o F had a post-treatment day ) and AST of . All other labs were unremarkable. This was considered possibly drug related. No f/u information is available. There were no clinical correlates.

RPD 10mg (0335) - 43 y/o F had increase platelet count of and decreased hemoglobin and hematocrit levels of respectively, at the post-treatment day 3. Repeat test 2 days later was essentially unchanged. The patient had a low Hgb and Hct at baseline

Placebo: (0158) - 24 y/o female had a post-treatment glucose value of eight days after treatment with placebo. All other labs were normal. There were no clinical correlates.

Placebo: (0238) - 49 y/o M had proteinuria at the post-treatment visit, day 21. The urinalysis was repeated 13 days later and was normal. There were no clinical correlates.

Placebo: (0226) - 51 y/o F had an elevated alkaline phosphatase of at the post-treatment visit, day 7. A repeat test on day 20 was unchanged at All other labs were normal.

## *8.6.2 Analysis of Central Tendencies*

The sponsor analyzed mean changes in all laboratory parameters tested and tabulated the results in the study report for Study 039, Table 49, page 16051, which I do not reproduce here. I reviewed these changes and all were minor and clinically insignificant.

## *8.6.3 Outliers*

"Clinically significant laboratory abnormalities" (outliers) were identified based on deviations of laboratory parameters from pre-defined normal ranges. These are listed in Table 14 (ISS Table D-113, page D-365).

***Table 14: Key to Potentially Clinically Significant Laboratory Abnormalities***

| Laboratory Test | Criteria for pCSLAs | FDA Criteria for Potentially CSLA | Lower Limit of Normal (LLN) | Upper Limit of Normal (ULN) |
|---|---|---|---|---|
| SGOT (male) | >=300% ULN | 3 x ULN | | |
| SGOT (female) | >=300% ULN | 3 x ULN | | |
| SGPT (male) | >=300% ULN | 3 x ULN | | |
| SGPT (female) | >=300% ULN | 3 x ULN | | |
| Alkaline Phosphatase | >=300% ULN | 3 x ULN | | |
| Creatinine | >=143% ULN | 2 mg/dL | | |
| Bilirubin (total) | >=167% ULN | 2 mg/dL | | |
| Hematocrit (male) | <=95% LLN | 37 % | | |
| Hematocrit (female) | <=94 % LLN | 32 % | | |
| Hemoglobin (male) | <=90% LLN | 11.5 gm/dL | | |
| Hemoglobin (female) | <=82% LLN | 9.5 gm/dL | | |
| WBC (elevated) | >=149 % ULN | 16 x $10^3$/uL | | |
| WBC (reduced) | <=64% LLN | 2.8 x $10^3$/uL | | |
| Eosinophils (increased) | >=147% ULN | 10 % | | |
| Neutrophils (decreased) | <=37% LLN | 15 % | | |
| Platelets (elevated) | >=178 % ULN | 700,000 x $10^3$/uL | | |
| Platelets (decreased) | <=58% LLN | 75,000 x $10^3$/uL | | |
| Sodium (increased) | >=105 % ULN | 155 mEq/L | | |
| Sodium (decreased) | <=95% LLN | 125 mEq/L | | |
| Potassium (increased) | >=111% ULN | 6 mEq/L | | |
| Potassium (decreased) | <=88% LLN | 3 mEq/L | | |

The core tabulation of pCSLAs is from patients in extensions of Phase III (acute).
[1]Criteria for CSLA increases are computed as: [FDA criteria for CSLA ÷ SciCor ULN] x 100.
Criteria for CSLA decreases are computed as: [FDA criteria for CSLA ÷ SciCor LLN] x 100.

The listing of all outliers are shown in Table 15 (ISS Table D-149, page D-483). A total of four patients were identified using the above criteria, 2 in the placebo group and 1 each in the 5mg and 10mg groups. There were no clinical correlates to any of these changes. A brief narrative of each case is provided below:

RPD 5mg: (0386) - 42 y/o F had a total WBC of 8 days after treating a migraine with RPD 5mg. A repeat test 20 days after dosing revealed a normal WBC count at . The baseline WBC was

RPD 10mg: (0335) - 43 y/o F had an elevated platelet count of 1045K, decreased Hgb at and decreased HCT of She had abnormal counts at baseline as well and were not considered significantly changed (also listed as an LAE in previous section).

Placebo: (0177) - 46 y/o M had a Hct of 7 days after treating a migraine attack with placebo. His baseline was and the post-treatment value was not considered significantly different from baseline.

Placebo: (0161) - 37 y/o F had an increase eosinophil percentage at baseline which increased 6 days after treatment with placebo to

***Table 15: Study 039 - Potentially Clinically Significant Laboratory Abnormalities***

| Laboratory Test | CSLA Criteria | Treatment | Allocation Number/ Study | Baseline Value | Post-Rx Value |
|---|---|---|---|---|---|
| Hb | <82% LLN (female) | RPD 10mg | 0335/ 039- 011 | | |
| HCT | <94% LLN (female) | RPD 10mg | 0335/ 039- 011 | | |
| | < 95% LLN (male) | PBO | 0177/ 039- 007 | | |
| Eosinophils | >147% ULN | PBO | 0161/ 039- 006 | | |
| WBC Count | <64% LLN | RPD 5mg | 0386/ 039- 003 | | |
| Platelets | >178% ULN | RPD 10mg | 0335/ 039- 011 | | |

## *8.7 Vital Signs*

Vital signs were recorded at pre-study, pre-treatment, and post-treatment in phase 1 studies and at pre-study and post-treatment in study 039.

### *8.7.1 Vital Signs Adverse Events*

No subjects or patients in phase 1 or phase 3 studies had an adverse experience found on vital signs (determined by the investigator).

### *8.7.2 Analysis of Central Tendencies*

Sponsor Table 16 (NDA Table C-66, page C-229), lists mean BP changes in patients exposed to study medications.

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***Table 16: Mean Changes in Blood Pressure***

| | Unit | Dose | Baseline N | Baseline Mean | Baseline SD | Treatment N | Treatment Mean | Treatment SD | Change N | Change Mean | Change SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SBP | mm | RPD 5mg | 100 | 116.5 | 12.96 | 100 | 115.5 | 13.16 | 100 | -1.03 | 9.3 |
| | | RPD 10mg | 113 | 117.0 | 12.93 | 113 | 116.0 | 13.00 | 113 | -1.03 | 12.12 |
| | | Placebo | 97 | 119.9 | 14.06 | 97 | 119.6 | 14.57 | 97 | -0.28 | 10.45 |
| DBP | mm | RPD 5mg | 100 | 75.03 | 8.66 | 100 | 74.98 | 8.12 | 100 | -0.05 | 7.78 |
| | | RPD 10mg | 113 | 74.58 | 9.00 | 113 | 74.59 | 8.86 | 113 | -0.01 | 7.59 |
| | | Placebo | 97 | 75.75 | 8.59 | 97 | 75.57 | 8.75 | 97 | -0.19 | 8.53 |

all measurement taken in the sitting position

The changes seen for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were small and clinically insignificant for all three treatments. Mean blood pressure parameters were unchanged or went down slightly in all cases.

Sponsor Table 17 (NDA Table C-67, page C-229) lists the mean changes in pulse. There were minor increases in mean pulse seen in all three groups but these are not clinically relevant.

*Table 17: Mean Changes in Pulse (Beats/Min)*

| | Baseline | | | Treatment | | | Change | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| RPD 5mg | 100 | 73.36 | 9.92 | 100 | 73.89 | 9.43 | 100 | 0.53 | 8.96 |
| RPD 10mg | 113 | 71.71 | 9.99 | 113 | 74.34 | 11.11 | 113 | 2.63 | 8.42 |
| Placebo | 97 | 72.15 | 8.79 | 97 | 73.14 | 10.36 | 97 | 0.99 | 7.90 |

### *8.7.3 Outliers*

Pre-defined criteria were used to identify BP outliers:

- diastolic BP ≥105mm and change from baseline ≥15mm
- diastolic BP ≤50mm and change from baseline ≤15mm
- systolic BP ≥180mm and change from baseline ≥20mm
- systolic BP ≤90mm and change from baseline ≤20mm

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There were no BP outliers in phase 1 studies. There were three patients in study 039 who were outliers. One patient (039-003-0312) took 5mg and had a drop of systolic BP of 36mm . The second (029-006-0396) took 10mg and had a drop of diastolic BP of 18mm . The third patient (039-002-0030) took placebo and had a drop in systolic BP of 22mm None was serious.

There were no potentially clinically significant vital sign abnormalities of pulse.

### *8.8 ECG*

ECG's were collected at similar time points to vital signs. There were no ECG associated AE's in phase1 studies.

One patient in study 039 had an ECG adverse experience. This was a 47 y/o male (039-004-0081) who had nonspecific ST-T wave changes 2 days after treatment with placebo. This was not serious and did not result in discontinuation.

### *8.9 Withdrawal Phenomenon and Abuse Potential*

This section is taken from my review of the tablet. As a class, $5HT_{1D}$ agonists have not been associated with withdrawal phenomena. In three of the phase 3 controlled studies (022, 029, 030), safety evaluations were obtained days to a

week after acute dosing with rizatriptan. There were no systematic abnormalities observed or reported in post-study physical examination, history, vital signs, laboratory, or ECG evaluation. These data suggest that withdrawal or rebound phenomena are not observed.

Similarly, as a class, $5HT_{1D}$ agonists have not been associated with high abuse potential. Although no specific data addressing this issue with rizatriptan exist, it is notable that during the phase 3 extensions, the mean interdose interval of rizatriptan was approximately constant over the trials. Also, there were no clinical reports of drug-seeking behavior, systematic reports of lost prescriptions or inappropriate escalations of dosing, or other signs of psychological or physical addiction, withdrawal or rebound phenomena associated with rizatriptan.

### *8.10 Human Reproduction Data*

This section is also taken from the tablet NDA review. There were no studies conducted in pregnant women, and they were systematically excluded from clinical trials. Despite such precautions, several patients became pregnant during clinical studies. These are listed in Table 18 (ISS Table D-122, page D-399). All patients on rizatriptan presumably were exposed during the first trimester. The spontaneously aborted pregnancy on RPD is included in this table.

*Table 18: Pregnant Patients Who Received Rizatriptan or Control*

| Study Drug | WAES # | Study | ID | Age | Safety Results |
|---|---|---|---|---|---|
| Rizatriptan 5 mg | 96040937 | 022 014 | 4443 | 31 | Normal delivery |
| Rizatriptan 5 mg | 96119113 | 022 029 | 5136 | 33 | Ongoing, no known complications. |
| Rizatriptan 10 mg | 96041053 | 022 018 | 4550 | 44 | Normal delivery |
| Rizatriptan 10 mg | 96030565 | 022 002 | 4043 | 26 | Normal delivery |
| Rizatriptan 10 mg | 96119112 | 022 029 | 5124 | 39 | Ongoing, no known complications. |
| Rizatriptan 10 mg | 95121463 | 025 011 | 6400 | 27 | Normal delivery |
| Rizatriptan 10 mg | 96042547 | 025 013 | 6248 | 24 | Normal delivery |
| Rizatriptan 10 mg | 95081921 | 025 019 | 6373 | 22 | Normal delivery |
| Rizatriptan 10 mg | 96081518 | 022 020 | 4623 | 33 | Elective abortion |
| Rizatriptan 10 mg | 96119603 | 022 040 | 5384 | 36 | Unknown |
| Rizatriptan 10 mg | 96067913 | 030 010 | 8168 | 37 | Unknown |
| Rizatriptan 10 mg | 96081518 | 022 020 | 4623 | 33 | Elective abortion |
| Rizatriptan 10 mg | 96075180 | 029 003 | 9398 | 19 | Elective abortion |
| Rizatriptan 10 mg/1mg IV | 96070904 | 042 001 | 0122 | 19 | Elective abortion |
| Standard care | 96110834 | 022 012 | 4367 | 21 | Unknown |
| Standard care | 96020409 | 022 009 | 4267 | 30 | Lost to follow up |
| Standard care | 96031291 | 022 023 | 0199 | 23 | Normal delivery |
| 5 mg RPD™ | 96041079 | 039 010 | 0255 | 44 | Spontaneous miscarriage † |
| Blinded treatment | 96121709 | 046 003 | 0049 | 24 | Ongoing, no known complications |
| Blinded treatment | 97010982 | 046 015 | 0454 | 32 | Elective abortion |

† This patient is discussed in section 8.3, Serious Adverse Events, page 17.

Six patients carried the pregnancies to term without complications. Four individuals decided to abort the fetus electively for reasons unrelated to study drug exposure, and one patient exposed to the RPD aborted spontaneously (see

8.3, Serious Adverse Events, page 17). No adverse events have been reported for the 2 patients in rizatriptan tablets in which the pregnancy continue.

No cases of male or female infertility have been reported during rizatriptan development.

### *8.11 Overdose*

No overdose information is available for the RPD specifically. This section is taken from the tablet NDA review.

No intentional overdoses of rizatriptan were reported during clinical trials. In phase 2 trials, rizatriptan 40mg (administered as a single dose or as two 20mg doses given 2 hours apart) was generally well tolerated in 323 patients. However, somnolence and dizziness were common at this dose level and two patients experienced syncope. One syncopal episode was associated with a painful venipuncture and the second one was associated with micturition and neither was serious.

In a clinical pharmacology study, 12 subjects received 80mg. Two of the 12 experienced syncope and/or bradycardia. One of the subjects, a 29 y/o female, developed vomiting, bradycardia, and dizziness beginning 3 hours after receiving a total of 80mg rizatriptan administered over 2 hours. Bradycardia was followed by a 10 second period of AV dissociation, which was responsive to atropine. This occurred one hour after the onset of the other symptoms. The other case was a 25 y/o male who experienced transient dizziness, syncope, incontinence, and a 5 second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred 2 hours after the subject had received a total of 80mg rizatriptan administered over 4 hours.

Based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular events due to vasoconstriction (*e.g.*, angina) could occur. Since there is no known antidote for rizatriptan, standard treatment for overdoses is recommended. Based on the half-life of rizatriptan, clinical and electrocardiographic monitoring should be continued for at least 12 hours even if clinical symptoms are not observed. The effects of hemodialysis or peritoneal dialysis on serum concentration of rizatriptan are unknown.

### *8.12 Safety of RPD vs. Tablets*

In general, the RPD formulation was well tolerated and is comparable to the tablet in terms of safety in all clinical safety measures (adverse events, laboratory, vital signs, and ECG). The comparison of incidences of clinical adverse experiences must be taken in the context that there were ten-fold fewer patients contributing to RPD safety data than to the tablet safety database.

Sponsor Table 19 (NDA Table C-70, page C-236) lists the incidence of selected AE's (most common AE's plus chest pain) for both tablet and RPD.

*Table 19: Common AE's After a Single Rizatriptan Tablet or RPD*

| AE | Tablets (%) | RPD (%) |
|---|---|---|
| *Dizziness* | | |
| Placebo | 5 (3) | 7 (7) |
| 5 mg | 4 (4) | 9 (9) |
| 10 mg | 9 (8) | 13 (12) |
| *Somnolence* | | |
| Placebo | 4 (3) | 6 (6) |
| 5 mg | 4 (4) | 4 (3) |
| 10 mg | 8 (8) | 4 (4) |
| *Asthenia/ Fatigue* | | |
| Placebo | 2 (1) | 1 (1) |
| 5 mg | 4 (3) | 2 (2) |
| 10 mg | 7 (5) | 2 (1) |
| *Nausea* | | |
| Placebo | 4 (3) | 8 (8) |
| 5 mg | 4 (3) | 7 (7) |
| 10 mg | 6 (4) | 13 (12) |
| *Dry Mouth* | | |
| Placebo | 1 (1) | 2 (1) |
| 5 mg | 3 (3) | 12 (12) |
| 10 mg | 3 (2) | 7 (7) |
| *Vomiting* | | |
| Placebo | 2 (< 1) | 1 (1) |
| 5 mg | 2 (1) | 1 (0) |
| 10 mg | 2 (1) | 4 (3) |
| *Chest Pain* | | |
| Placebo | 1 (1) | 1 (1) |
| 5 mg | 2 (2) | 2 (2) |
| 10 mg | 3 (3) | <1 (0) |

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Nausea and dizziness occurred in both formulations at incidences of ≥5% and were comparable to each other when placebo was taken into account. However, somnolence and asthenia/fatigue, relatively common AE's with tablet, were less common in patients treated with RPD. Dry mouth appears to be more common with RPD.

### *8.13 Summary of Key Adverse Events*

The most common AE's seen with RPD (occurring ≥5%) were nausea, dizziness, and dry mouth. The adverse events seen with the RPD appear to be similar to those seen with the tablet. Dry mouth appears to be more common with RPD, although this uses historical controls.

### *8.14 Safety Conclusions*

Based on the safety data presented,

1. Rizatriptan 5mg RPD and 10mg RPD are generally safe and well tolerated.
2. The most common AE's were nausea, dizziness, and dry mouth and are similar to those seen with the tablet formulation.

## 9. Four Month Safety Update

No new data on the RPD formulation was received on case report forms in the four months after the NDA cutoff date. Therefore, the four month safety update contains information only for the tablet. I refer the reader to my review of the tablet NDA for a review of this material.

## 10. Labeling Review

The sponsor combines the labeling for rizatriptan tablets with that for the rapidly disintegrating tablet (RPD). I include comments pertinent to both tablet and RPD in this section. The comments for the tablet portion of labeling are also contained in my review of the tablet NDA (20-864).

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DRAFT LABELING

## 11. Conclusions

In my opinion, rizatriptan 5mg and 10mg RPD are safe and effective on an intermittent, outpatient basis for the treatment of acute migraine headache. There is little evidence that 10mg is any better than 5mg. There is evidence that 10mg is associated with a higher incidence of adverse events, although not alarmingly so. There may be individual patients who benefit from the higher dose.

There is no evidence that the RPD provides any faster or greater relief than the tablet. In fact, the $T_{max}$ of the RPD is longer compared to the tablet $T_{max}$. It appears that the RPD is a reasonable alternative to the tablet in patients who have no liquids available to them at the time of a migraine attack, or in patients who prefer the RPD formulation.

## 12. Recommendations

NDA 20-768 is approvable with appropriate changes to proposed labeling, as described in my labeling review in section 10.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. /S/ (see memo)

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# Appendix A - Efficacy Study 039

## *12.1.2 Title*

A Randomized, Triple-Blind, Placebo-controlled, Parallel Groups, Outpatient Study to Examine the Safety, Tolerability, and Efficacy of MK-0462 10mg RPD (Benzoate Salt) and MK-0462 5mg RPD for the Acute Treatment of Migraine (Protocol 039).

## *12.1.3 Study Centers*

12 Centers in the United States

## *12.1.4 Objective*

- To examine the efficacy of rizatriptan 5mg and 10mg RPD for the acute treatment of migraine
- To examine the safety and tolerability of 5mg and 10mg RPD for the acute treatment of migraine

## *12.1.5 Design*

This was a randomized, triple-blind, placebo-controlled, parallel groups study.

## *12.1.6 Duration*

1 day. The study was conducted between 2/96 - 6/96.

## *12.1.7 Setting*

This was an outpatient study.

## *12.1.8 Sample Size*

381 migraine patients enrolled, of which 312 took study medication and 310 completed the study.

## *12.1.9 Selection*

### *12.1.9.1 Key Inclusion Criteria*

- male or non-pregnant female, years old, with at least a 6 month history of migraine (IHS criteria), with 1-8 migraines per month

### *12.1.9.2 Key Exclusion Criteria*

- basilar or hemiplegic migraine
- significant medical illnesses (including heart, kidney, liver, neurological, endocrine, gastrointestinal, hypertension)
- pregnancy or nursing

### *12.1.9.3 Concomitant Medications*

Not allowed:
within 2 weeks: MAO inhibitors, methysergide, or lithium
within 48 hours: any ergot derivative, sumatriptan, or Midrin
within 24 hours: any opiate

within 6 hours: analgesic, antiemetics

*12.1.10 Dosage*

Rizatriptan RPD 5mg
Rizatriptan RPD 10mg
Placebo



*12.1.11 Schedule*

After screening, eligible patients were randomized to receive rizatriptan 5mg, rizatriptan 10mg, or placebo for initial treatment of a grade 2 or 3 migraine headache. Patients rated headache severity, functional disability, and associated migraine symptoms at baseline and again at 0.5, 1, 1.5, 2,3, and 4 hours post dose. A "satisfaction with medication" questionnaire was filled out at 2 hours.

Up to two treatments for recurrence were allowed within 24 hours. These were not randomized and were identical in dose and appearance to the initial treatment.

Escape medication was permitted after 2 hours for persistent headache and/or recurrence. A second dose of study medication was not given. The time to recurrence was also recorded.

Patients returned to the clinic within 7 days of treatment for a follow-up assessment.

*12.1.12 Outcome Measures*

The primary outcome measure was the headache response rate at 2 hours post-dose, measured in the traditional manner, using a 4 point headache scale (0-3 for none, mild, moderate, severe). A responder was classified at a patient with a grade 2 or 3 headache at baseline and a grade 0 or 1 headache at 2 hours.

Secondary endpoints included the complete headache relief rate at 2 hours, absence of associated symptoms at 2 hours (nausea, vomiting, photophobia, phonophobia), absence of functional disability at 2 hours, and need for rescue after initial dose.

Additional secondary endpoints included the rates of taste acceptability, and formulation preference (between RPD and historical controls for tablet).