CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20864/20865

MEDICAL REVIEW(S)

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 18, 1998

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable Actions:
NDA 20-864 for Maxalt (rizatriptan benzoate) Tablets
NDA 20-865 for Maxalt (rizatriptan benzoate) RPD

TO: File NDAs 20-864 & 20-865
&
Robert Temple, M.D.
Director, ODE1

APPEARS THIS WAY
ON ORIGINAL

This memorandum conveys to the file my recommendation, offered as Director of the Division responsible for the review of these applications, that the NDAs for Maxalt Tablets and Maxalt RPD (an oral formulation that disintegrates immediately in the mouth), be approved for use in the management of migraine headache.

Dr. Randy Levin, a team leader in the Division's neurology unit, led the review effort and served as the Division's lead negotiator in the iterative interactions that have led to the development of Maxalt product labeling acceptable to both the Division and the sponsor. Dr. Levin has produced a comprehensive overview and analysis of both applications (documents for both the tablet and RPD are dated 6/9/98). Dr. Armando Oliva is the primary clinical reviewer (3/25/98 tablet and 4/2/98 RPD). The basic pharmacology review was conducted by Dr. Tom Steele (4/20/98 tablet and 5/7/97 RPD). The statistical consultative review of lifetime in vivo CA studies in both rats and mice was performed by Kooros Mahjoob, PhD. (4/8/98) Dr. Glenna Fitzgerald provides a supervisory overview of the two NDAs in a 6/4/98 memorandum. The PDUFA action date is 6/30/98

The drug substance

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Rizatriptan, the active component of each product, is a 5-$HT_{1B/1D}$ agonist

ligand; a number of other drugs with this receptor binding activity are currently marketed for the treatment of migranine by both parenteral (e.g. sumatriptan) and oral routes (e.g. sumatriptan, zolmitriptan, naratriptan.). 5-$HT_{1B/1D}$ agonists are presumed to attenuate the duration and severity of acute migraine attacks through their capacity to 1) constrict smooth muscle in the walls of dilated meningeal blood vessels [5-HT_{1B} receptor] and 2) inhibit the release of various chemical mediators of inflammation from prejunctional terminals of the trigeminal nerve [5-$HT_{1B/1D}$].

ADME

The following tables, reproduced from page 4 of Dr. Levin's 6/9/98 review of the tablet NDA, nicely summarizes the biopharmacokinetic properties of rizatriptan:

PK information	
Absorption	
Absorption	90% absorbed
Bioavailability	40 to 45% (tablet and disk similar)
Tmax - oral	1 to 1.5 hours
Tmax - disk	1.6 to 2.5 hours
Food effect	no change in bioavailability, delayed Tmax by 1 hour
PK	AUC and Cmax increased slightly more than proportionately with doses of 2.5 to 15 mg.
AUC	30% higher in females
Accumulation	no accumulation was seen with dosing of three doses of 10 mg for 4 consecutive days
Distribution	
Protein binding	14%
Volume of distribution	140 liters in males and 110 liters in females
Metabolism	
main route	oxidative deamination by MAO-A
metabolites	N-monodesmethyl 14% of parent- active at 5HT site
urine	14% excreted in the urine unchanged, 51% excreted as indole acid metabolite consistent with first pass metabolism, 80% excreted in the urine
liver	10%
half life	2 to 3 hours
half life of metabolites	6 hours
P450	not an inhibitor of P450 from in vitro testing

Special populations	
renal impairment	AUC only affected in patients undergoing hemodialysis with a 44% greater AUC
hepatic impairment	20% decrease in clearance in patients with mild to moderate hepatic failure
Age	plasma concentrations similar, renal clearance lower
Sex	30% increase in AUC, 11% increase in Cmax
Race	no effect
Drug interactions	
Oral contraceptive	no effect on plasma concentrations
Propranolol	rizatriptan AUC increased 70%
MAO A inhibitors	rizatriptan AUC and Cmax increased by 120% and 40% respectively
Nadolol/metoprolol	no effect
Paroxetine	no effect

The preceding tables are derived from one that appears in Dr. Levin's review for the Tablet; the ADME of the orally disintegrating formulation is said generally to be similar (bioequivalent in one study, and not in another). Although perhaps a counter-intuitive finding, the Tmax for the tablet is actually shorter than that of the RPD formulation. The explanation lies presumably in the fact that the tablet reaches the small intestine faster on average than the solution of rizatriptan that is formed when the RPD formulation is placed on a mucosal surface in the oral cavity.

It is of note that the product is metabolized via oxidative deamination catalyzed by MAO, type A, and not via a P450 enzyme system. At very high concentrations rizatriptan exhibits some capacity to inhibit P450 2D6, but this is thought to have little, if any , potential clinical significance.

Effectiveness in Use

As is the case with most drugs in the class, the effectiveness of the rizatriptan (both as a tablet and as an orally disintegrating dosage formulation) was unequivocally and robustly demonstrated in several adequate and well controlled clinical trials.

Treatment response in virtually every study was evaluated by comparing, 2 hours after drug administration, the percentage of responding patients

within groups assigned to placebo and to one or more dose levels rizatriptan A patient entering the study with moderate to severe headache (i.e., score of 3 or 4) was declared a responder if, at two hours, his/her symptoms had abated completely (a score of 0), or persisted , but at a mild level (score of 1).

Beyond establishing the effectiveness of rizatriptan, the controlled trials provide information about the dose response relationship The following table is taken from Dr. Levin Tablet review (page 12)

Table: Response rates 2 hours following treatment of initial headache (n=number of patients)

Study	Placebo	2.5 mg	5 mg	10 mg	20 mg	40 mg	Sumatriptan[1]
004	33% (n=21)				50% (n=8)	75%* (n=36)	
008	18% (n=85)			52%* (n=89)	56%* (n=82)	67%*† (n=120)	46%* (n=72)
014	18% (n=67)	21% (n=75)	45%* (n=130)	48%* (n=145)			
020[2]	33% (n=38)			54% (n=99)			
022	35% (n=304)		62%* (n=458)	71%*# (n=456)			
025[3]	37% (n=82)			77%* (n=320)			
029	23% (n=80)		63%* (n=352)				67%* (n=356)
030	40% (n=159)		60%* (n=164)	67%* (n=385)			62%* (n=387)

*p value < 0.05 in comparison with placebo
#p value < 0.05 in comparison with 5 mg
†p value < 0.05 in comparison with sumatriptan
[1]Sumatriptan dose was 100 mg in all studies except 029 where the dose was 50 mg.
[2]This was the only study in which patients treated the headache in a clinic setting (no statistical tests were reported)
[3]Results for initial headache only.

It is of note that absolute response rates vary among studies, but that in general, over the range of 2.5 to 40 mg single doses, the proportion of patients responding tends to increase with dose and is always greater than the proportion responding to placebo. In study 022 where the sample size was quite large (circa 450 per group), a statistically significant difference in response rates was shown between groups assigned to 5 mg

and 10 mg doses. The reciprocal of the difference in proportion responding on drug versus placebo is a measure of the drug's effect expressed in terms of the number of subjects that must be treated to have one subject gain the response defined (i.e., in this case no or only a mild residual headache.

Number needed to treat to get one response								
study #	Dose mg placebo fraction	3	5	10	20	40	Imi	
004	0.33				5.9	2.4		
008	0.18			2.9	2.6	2	3.6	
014	0.18	33	3.7	3.3				
020	0.33			1.9				
022	0.35		3.7	2.8				
025	0.37			2.5				
029	0.23		2.5				2.3	
030	0.4		5	3.7			4.5	

The re-expressed outcomes again reveal that an increase in dose is associated within any trial with multiple doses (i.e., 004, 008, 014, 022, 030) with an increase in the proportion responding to that dose. It is also clear, however, that the absolute response among studies is not an obviously predicted by either dose or the placebo response rate in a study. This illustrates, once again, the futility of attempting to compare effect sizes across trials.

Additional analyses show that dose also affects the probability that a patient will require re-medication during the first 24 hours following initial treatment. (See figure 13 on page 13 of Dr. Levin's 6/9/98 review.)

Finally, I note that in the single placebo controlled trial of the orally disintegrating dosage formulation, the response rate of the groups assigned to 5 and 10 mg are essentially identical. I am not troubled by this failure in that a 10 mg dose is reasonably safe, although I am still unsure why the sponsor seeks to market a formulation that may perform less reliably than a traditional tablet. I am mindful, of course, that some patients may find it difficult to swallow a solid oral dosage formulation,

and, for them, I grant, the orally disintegrating formulation would be a convenience.

Safety for Use

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Preclinical

There are no preclinical findings of concern. In fact, in Dr. Fitzgerald view, Maxalt is a relatively "clean" compared to other drugs of the class (June 4, 1998). Both Dr. Steele and Dr. Fitzgerald have, however, made a number of suggestions concerning the precise wording of labeling statements.

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Clinical

Some 300 healthy volunteers and 3700 migraineurs have been exposed to at least 1 dose of rizatriptan. According to Dr. Levin, the numbers of patients receiving the drug in phase 2/3 trials at doses within or above the proposed dosing range are 1165 at 5 mg, 1180 at 10 mg and 492 at higher doses. In addition, the ICH guidance standard for 6 month and 1 year exposures has been satisfied[1] for both the 5 and 10 mg doses .

The reports of adverse events from this experience are typical of a drug of the therapeutic class

Accordingly, although no drug is risk free, the risks of rizatriptan are, by current agency standards, acceptable in a drug intended for the treatment of acute migraine attacks.

Labeling

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As a result of his negotiations with the firm, Dr. Levin has been able to develop labeling that in my opinion not only meets the requirements of

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[1] Because of the intermittent use, divisional rules for determining whether or not a patient has been exposed chronically are used, that is, a patient does not qualify unless over the nominal interval of use, 2 or more headaches have been treated per month on average over that interval

law, but conforms fully with the form of labeling the Division and Office have applied to other recently approved anti-migraine drug products.

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Conclusion

Within the meaning of the Act, Maxalt and Maxalt RPD have been shown to be safe for use and effective in use.

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Recommendation

The NDAs for Maxalt Tablets and Maxalt RPD should be approved under the labeling attached to the approval action letter being forwarded to the Office for signature.

/S/

Paul Leber, M.D.
June 18, 1998

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cc NDAs 20-864 and 20-865
HFD-101
Temple
HFD-120
Katz
Levin
Oliva
Steele
Fitzgerald
Bates
Seevers
Chen
HFD-710
Hoberman
HFD-860
Sahajawalla
Tammara

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ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: June 9, 1998
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-865 Maxalt RPD
To: file

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INTRODUCTION

The sponsor submitted two NDAs for Maxalt (rizatriptan). NDA 20-864 was for a tablet formulation. NDA 20-865 is for a oral formulation that dissolves on the tongue. The sponsor calls this formulation rapidisc (RPD). The advantage of this formulation over the tablet is that patients do not need to take liquids with the disks.

The sponsor has submitted three studies for this NDA and refers to NDA for supporting material. Two studies, 033 and 04, are phase 1 PK and bioavailability studies, respectively. The third study, 039, is a safety and efficacy study.

The review team for the tablet and this NDA is the same as for NDA

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CHEMISTRY, MANUFACTURING AND CONTROLS

Dr. Bates and Dr. Seevers were the reviewers for the CMC section. They recommended approval of the drug. The name of the formulation, rapidly disintegrating tablet was changed to orally disintegrating tablet to avoid misleading prescribers and patients in thinking that the rapid referred to onset of action. There were no outstanding issues.

APPEARS THIS WAY ON ORIGINAL

PRECLINICAL TOXICOLOGY

Dr. Tom Steele, Dr. Fisher and Dr. Fitzgerald were the toxicology reviewers. They recommended approval. They recommended that the drug be classified Category C for use during pregnancy. See the memo for NDA 20-864 for additional discussion on this issue. There were no outstanding issues.

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BIOPHARM

Dr. Veejay Tammara and Dr. Chandra Sahajwalla were the biopharm reviewers. They recommended approval of the drug. See the memo for NDA 20-864 for a summary of the PK of the drug in comparison with the tablet. There were no outstanding issues.

EFFICACY

Dr. Armando Oliva reviewed the efficacy data with Dr. Hoberman as the statistical consultant.

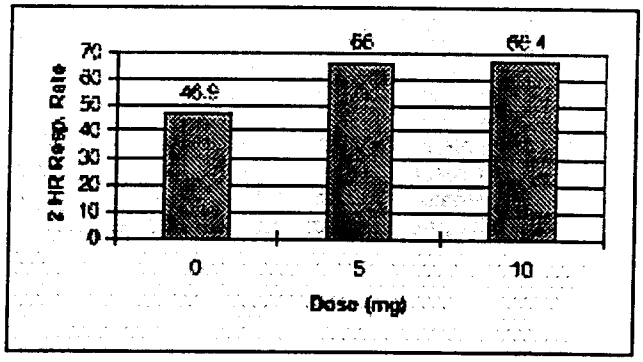
The evidence for the efficacy of the tablet formulation in the acute treatment of migraines was provided in NDA The sponsor has provided a single efficacy study, 039, supporting the efficacy of the disk formulation.

Study 039 was an adequate and well controlled study similar in design to recent migraine trials including those provided for the tablet formulation. Study 039 was a randomized, double blind, placebo controlled, parallel study evaluating doses of 5 and 10 mg for the acute treatment of migraines in an outpatient setting. Patients were instructed to treat a moderate to severe headache with the study medication. The patients were allowed to remedicate up to two recurrences within 24 hours. Rescue was allowed 2 hours after the initial treatment. The primary outcome was the headache response rate 2 hours following treatment. Headache response is defined as headache pain reduced from moderate or severe to mild or no pain. The sponsor also assessed the presence or absence of associated migraine symptoms, need for rescue and the "functional disability" as secondary outcome measures.

312 patients took treatment with 100 randomized to 5 mg, 114 to 10 mg and 98 to placebo. The mean age was 39.9 with 88% of the patients being female and over 90% being white. Approximately two thirds of the patients had moderate headaches at baseline.

There was a statistically significant higher headache response rate in patients taking either the 5 or 10 mg disks compared to placebo. The rates are summarized in figure 2 from Dr. Oliva's review.

Figure 2: Study 039 - Two Hour Headache Response Rate



The response rates at the other time points are summarized in the following table

Response rates (%) following treatment						
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*

*p value < 0.05

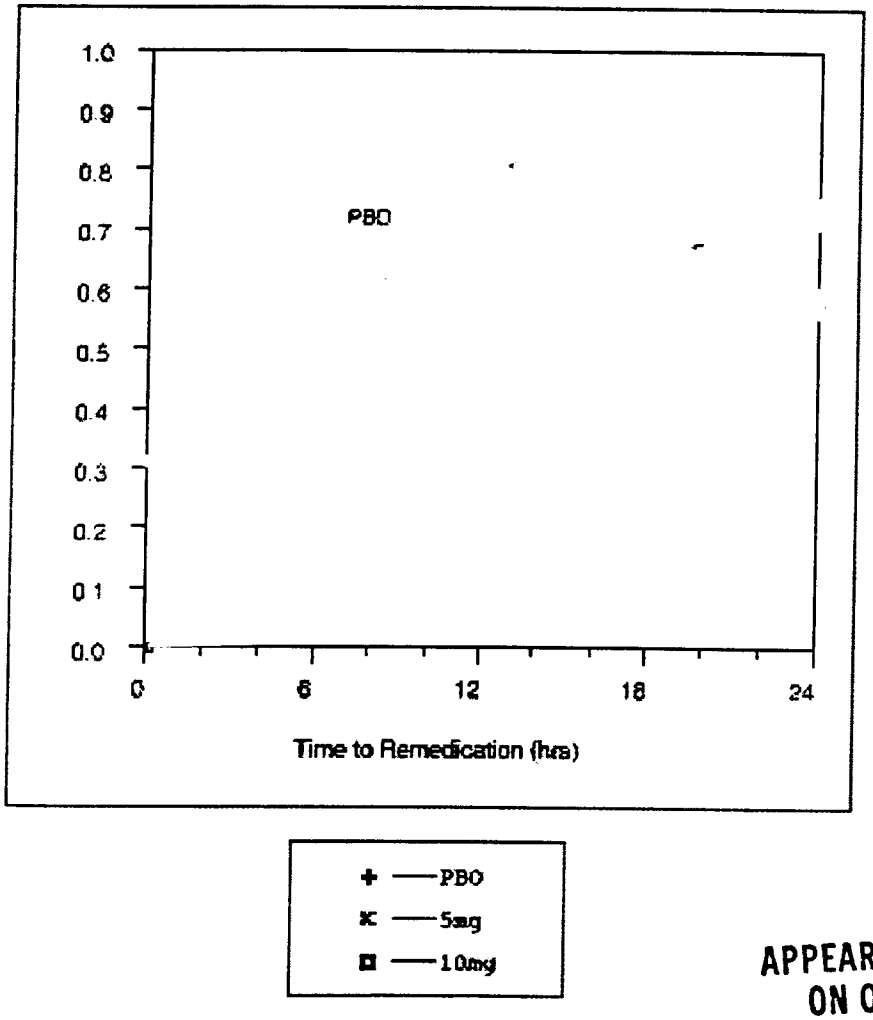
The percentage of patients who were pain free 2 hours following treatment was greater in the 5 and 10 mg group compared to placebo ($p < 0.05$).

The absence of associated symptoms of nausea, photophobia and phonophobia numerically favored the active treatment groups. A comparison of the incidence of photophobia and phonophobia was associated with a p value of < 0.05 for both the 5 and 10 mg. The incidence of nausea while lower in the active treatment groups was not associated with a p value < 0.05 when compared to placebo.

There were no significant effects on efficacy related to sex of the patient, age, aura, use of migraine prophylaxis or use of contraceptives. The number of non white patients was too small to assess.

Dr. Oliva calculated the time to remedication up to 24 hours following dosing and summarized the findings in a Kaplan Meier plot (figure 4). Patients were allowed to take rescue 2 hours after dosing.

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



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.

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).

SAFETY

There were no deaths . No patients discontinuations for adverse events. There were two serious adverse events reported both for abortions. One was an elective abortion and the second was a spontaneous abortion. The spontaneous abortion occurred in a 44 year old patient who treated a single migraine with 5 mg on 3/1/98. The abortion occurred on 4/22/98. The adverse events reported were similar to those reported for the tablet. There was a slight increase in the incidence of nausea (4% vs 12%) and dry mouth (2% vs 7%) with the 10 mg RPD compared to the 10 mg tablet.

There was no long term experience with the RPD formulation.

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Reviewer's conclusions:

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.

Team Leader's conclusions:

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The safety data does not appear to differ significantly from the tablet data. The reliance on the long term safety data obtained from the tablet is adequate with the assumption that there are no long term local effects from the RPD.

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ON ORIGINAL

RECOMMENDATIONS

In this NDA, the sponsor has provided evidence for the efficacy and safety of the orally disintegrating tablet from a single study. Ordinarily, evidence for efficacy would need to come from more than one study and evidence for safety would need to come from experience from not only single dose studies but long term studies where the drug is used repeatedly. I feel that the evidence supplied in NDA 20-864 on the tablet formulation of Maxalt is adequate to support the safety and efficacy of the orally disintegrating tablet. NDA 20-864 provided evidence from more than one adequate and well controlled study that the drug is effective for the acute treatment of migraine headaches. There also was evidence for the safety of Maxalt as provided in adequate safety data for the evaluation of the short term and long term safety of the drug. This evidence suggests that the drug is as safe as other drugs in its class that are currently marketed for this indication.

The attached labeling is consistent with labeling for other drugs in this class. The original name of the drug, rapidly disintegrating tablet and rapidisc (RPD) was potentially misleading as it represented the drug as working more rapidly than the tablet formulation. Not only has the rapidisc not been shown to work faster than the tablet but it has been shown to have a longer Tmax. The sponsor has changed the name of the formulation to orally disintegrating tablet and has changed the trademark to Maxalt MLT. In their initial printing of package labeling, the name Maxalt will be used. In subsequent printing Maxalt MLT will be used.

The package insert for the Maxalt tablet and Maxalt MLT will be the same. A single patient package insert will be used and will include special instructions for the use of the orally disintegrating tablet.

The sponsor is agreeable to the labeling except for three parts related to preclinical issues. First, the sponsor wants the drug classified as category B in regards to the safety for use of Maxalt during pregnancy and our reviewers feel that the drug should be category C. There does not appear to be a significant dispute with the findings of the reproductive toxicity studies. There was a reduction in weight in the offspring that occurred in the absence of maternal toxicity. The sponsor feels that the weight loss was transient but our reviewers note that the reduction in weight gain was seen both pre and post weaning. There is a dispute on the adequacy of the dose used in the studies. The sponsor feels that a dose the maximum recommended dose in humans is adequate. Our reviewers feel that since there are differences in the way that the drug is handled between species that dose, in itself, is not adequate to determine the proper dose. The dose is better determined by the presence of maternal toxicity which is a better indicator of drug effect than the magnitude of the dose used in humans. (It should be noted that the dose of 100 mg/kg/day was minimally toxic in other studies). The findings for Maxalt do suggest that the drug may have less fetal toxicity than seen with other drugs in this class, but the full spectrum of the developmental toxicity of the drug is not known since the developmental and reproductive toxicity studies did not use higher doses. In a dose finding study where higher doses were used (>=250 mg/kg/day), there was an increase in pup mortality rates. In the confines of the current classification system, I agree with our reviewer's recommendations that the category C is justified because of the finding of decreased weight, the suggested toxicity at higher doses and the lack of evaluation at adequately high doses.

Second, the sponsor wanted to describe two developmental toxicity studies. We included only one study because the second study involved a degradant.

Third, the sponsor wants to include results from albino rat and mouse study to address a potential concern for eye damage because the drug binds to melanin. These studies are not relevant to the problem since these animals do not have melanin. Other sponsors performed studies in pigmented animals.

There are no other outstanding issues.

I recommend that the drug be approved with the attached labeling.

/S/

Randy Levin, M.D.
Neurology Team Leader
RI/June 9,1998

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: June 9, 1998
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-864 Maxalt Tablets (rizatriptan)
To: file

Table of contents:

Introduction:

Merck submitted NDA 20-864 on 6/30/97 (6/30/98 is the PDUFA due date) for Maxalt (rizatriptan) tablets for the indication of acute treatment of migraine headaches. At the same time, the sponsor also submitted NDA 20-865 for Maxalt Rapidisc (rizatriptan rapid dissolving disks) for the same indication. This drug was evaluated under IND

During the development of rizatriptan, there were two issues raised concerning the rapid disk formulation, one concerned a waiver on imprinting on the rapid disk formulation, a waiver was not granted and the second concerned the need to further characterize a degradant found in the rapid disk formulation. There were no specific issues regarding the tablet formulation.

The review team consisted of Lana Chen, (project manager), Dr. Doris Bates (chemistry, manufacturing and controls), Dr. Tom Steele (preclinical pharmacology and toxicology), Dr. Vijay Tammara, (clinical pharmacokinetics), Dr. Armando Oliva (clinical safety and efficacy, and Dr. David Hoberman (statistical analyses).

CMC

The CMC section was reviewed by Dr. Doris Bates and Dr. Robert Seevers. They found the CMC information adequate for the recommendation of approval of the drug. There are no outstanding issues.

Preclinical safety

Dr. Tom Steele and Dr. Glenna Fitzgerald reviewed the preclinical safety section and found the information adequate to recommend approval of the drug. There are no outstanding issues.

The sponsor proposed to rate Maxalt as category B for use in pregnancy. The pharmtox reviewers including Dr. Fisher evaluated the sponsor's proposal and justification for the pregnancy rating and found it inadequate for a category B rating.

The toxicology reviewers found that it was difficult to determine the safety of Maxalt in pregnancy because the sponsor did not adequately assess the potential for developmental neurotoxicity. Developmental neurotoxicity is commonly assessed using neurobehavioral testing. While the sponsor did perform neurobehavioral studies in a fertility study, the validity of the results are in question because the doses used were inappropriately low because they failed to reach maternal toxicity. The sponsor argued that the doses were adequate based on multiples of the doses recommended in labeling but because there are differences between species, the toxicology reviewers base the adequacy of the doses on maternal toxicity.

The highest doses evaluated in any of the definitive rat reproductive/developmental toxicity studies were marginal since much higher doses were well tolerated in dose range-finding studies. In the studies using the higher doses, there was an effect on growth and survival. Growth retardation, a consistent finding in rats, can be a sensitive indicator of

developmental toxicity. For Maxalt, the risk for developmental toxicity is indicated because this developmental effects was seen at doses below those that were maternally toxic.

Because of the finding of growth retardation and lack of neurobehavioral tests performed at adequate doses, the recommendation is to label rizatriptan Pregnancy Category C.

Pharmacokinetics

Dr. Veejay Tammara and Dr. Chandra Sahajwalla reviewed the PK section and found the information adequate to recommend approval of the drug. There are no outstanding issues. They recommend that the sponsor evaluate interaction with drug that interfere with renal secretion (e.g., cimetidine).

A summary of the findings are summarized in the following table:

PK information	
Aborption	
Absorption	90% absorbed
Bioavailability	40 to 45% (tablet and disk similar)
Tmax - oral	1 to 1.5 hours
Tmax - disk	1.6 to 2.5 hours
Food effect	no change in bioavailability, delayed Tmax by 1 hour
PK	AUC and Cmax increased slightly more than proportionately with doses of 2.5 to 15 mg.
AUC	30% higher in females
Accumulation	no accumulation was seen with dosing of three doses of 10 mg for 4 consecutive days
Distribution	
Protein binding	14%
Volume of distribution	140 liters in males and 110 liters in females
Metabolism	
main route	oxidative deamination by MAO-A
metabolites	N-monodesmethyl 14% of parent- active at 5HT site
urine	14% excreted in the urine unchanged, 51% excreted as indole acid metabolite consistent with first pass metabolism, 80% excreted in the urine
liver	10%
half life	2 to 3 hours
half life of metabolites	6 hours
P450	not an inhibitor of P450 from in vitro testing
Special populations	
renal impairment	AUC only affected in patients undergoing hemodialysis with a 44% greater AUC
hepatic impairment	20% decrease in clearance in patients with mild to moderate hepatic failure
Age	plasma concentrations similar, renal clearance lower
Sex	30% increase in AUC, 11% increase in Cmax
Race	no effect
Drug interactions	
Oral contraceptive	no effect on plasma concentrations
Propranolol	rizatriptan AUC increased 70%
MAO A inhibitors	rizatriptan AUC and Cmax increased by 120% and 40% respectively
Nadolol/metoprolol	no effect
Paroxetine	no effect

Efficacy

Studies design

The efficacy of the drug was defined in 8 studies (004, 008, 014, 020, 022, 025, 029 and 030). Four studies (022, 025, 029 and 030) used the marketed formulation at the recommended doses in an outpatient setting. In all studies, patients with a moderate to severe migraine headache, were randomized to active treatments or placebo in a double blind fashion. Patients with a 6 month history of migraines with or without an aura were selected for the studies.

Study outcome measures

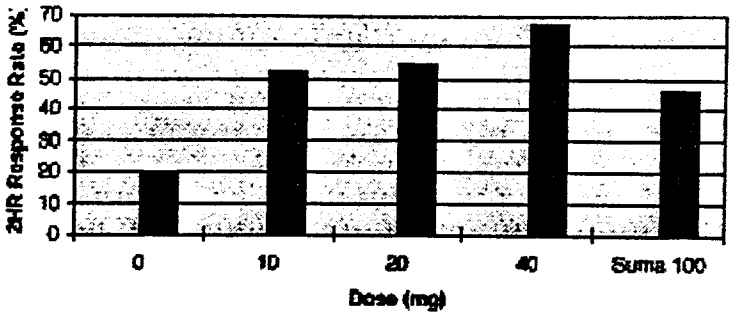
All studies examined the efficacy of a single dose. In two studies, the treatment of headache recurrence was also evaluated (022 and 025). In two studies, the efficacy of rizatriptan was compared to sumatriptan (029, 030). The primary outcome measure was the headache response rate defined as a change in headache severity from moderate or severe (score of 2 or 3, respectively) to mild or no headache (score of 1 or 0, respectively) 2 hours after treatment (escape medication was allowed after 2 hours). Patients assessed their headache severity at 0.5, 1, 1.5, 2, 3 and 4 hours. The presence or absence of associated migraine symptoms (nausea, vomiting, photophobia, and phonophobia , "clinical disability" (rated by the patient from normal, mildly impaired, moderately impaired, bedrest), time to headache response (029, 030), time to escape, headache recurrence (defined as a grade 2 or 3 headache within 24 hours of achieving a grade 0 or 1 headache at 2 hours), overall patients satisfaction and quality of life questionnaires were also assessed in one or more studies.

Dose ranging studies

In phase 1 studies, the sponsor noted increased blood pressure in subjects receiving doses of = 60 mg. **Study 004**, the initial dose ranging study was a small (65 patients) study evaluating doses of 0, 20 and 40 mg. The response rates were 33, 50 and 75% for the placebo, 20 and 40 mg doses, respectively.

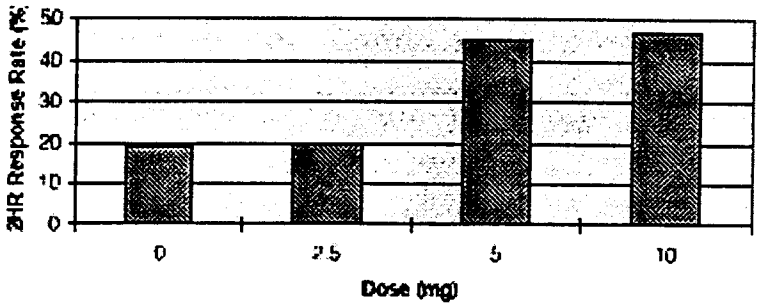
Study 008 was the second dose ranging study. 449 patients were randomized to doses of 0, 10, 20, 40 mg of rizatriptan or 100 mg of sumatriptan in a 1:1:1.5:1 ratio. The response rates for all doses were significantly higher in the active treatment groups compared to placebo. Numerically, the response rates were highest in the 40 mg dose group, followed by the 20 mg dose group and then the 10 mg dose group. Numerically, the 10 mg dose group and sumatriptan had similar results. Patients on the 20 and 40 mg doses had more adverse effects including dizziness and drowsiness. The response rates at 2 hours are summarized in figure 3 from Dr. Oliva's review.

Figure 3: Study 008, Dose-Ranging Study (N=449)



To evaluate the lower end of the response curve, the sponsor conducted **study 014.** 418 patients were randomized to doses of 0, 2.5, 5 or 10 mg in a 1:1:1.5:1.5 ratio. The 2.5 mg dose was not significantly different from placebo. The 5 and 10 mg doses did not differ significantly from each other. The response rates at 2 hours are summarized in figure 4 from Dr. Oliva's review. As in study 008, the formulation used in this study is not that proposed for marketing.

Figure 4: Study 014, Low Dose Ranging Study (N=419)



The effect of the 10 mg dose on ECG monitoring was evaluated in **study 020.** 132 patients were randomized to 0 or 10 mg in a 1:3 ratio. The response rate was significantly higher in the 10 mg group compared to placebo. A small number (n=25) of older patients (mean age 62) were enrolled in this study. . Because patients were intensely monitored for cardiac problems, determination of efficacy was not considered a primary objective. This study will be discussed in the safety review.

Phase 3 studies

The sponsor concluded from the dose ranging studies that doses of 20 mg and greater were less tolerated that doses of 2.5 mg and lower were ineffective. They elected to evaluate only the 5 and 10 mg doses in what they identified as the pivotal efficacy studies (022, 025, 029, 030).

All studies evaluated the efficacy of a single dose in the acute treatment of a single headache. Studies 022 and 025 also evaluated the treatment of headache recurrence. Study 025 evaluated the consistency of response over the treatment of 4 headaches. In studies 029 and 030, the efficacy of rizatriptan was compared to sumatriptan.

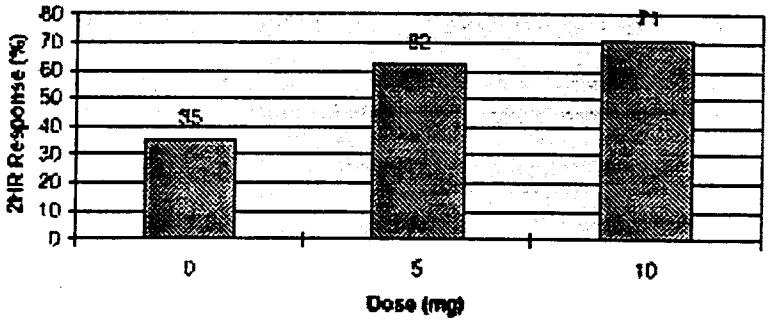
In these 4 studies, 2144 patients were treated with either 5 mg (977 patients) or 10 mg (1167 patients). An additional 627 patients were treated with placebo. In two studies, sumatriptan was included as an active control group (745 patients treated with sumatriptan). Approximately 85% of the patients were female with close to 90% white with a mean age of 40. About 85% had common migraines.

Study 022:

This was a multinational study evaluating the 5 and 10 mg dose for the treatment of a single migraine headache. Patients were randomized to 0, 5 or 10 mg of rizatriptan in a 1:1.5:1.5 ratio. 304 patients were randomized to placebo, 458 to 5 mg and 456 to 10 mg. The baseline characteristics were similar between groups. The 2 hour response rate is summarized by figure 6 from Dr. Oliva's review. A comparison of the rates for either the 5 and 10 mg groups with placebo were statistically significant. The difference between the 5 and 10 mg group was associated with a nominal p value of 0.007.

Patients were also randomized to receive their initial dose or placebo to treat recurrent headache pain. A recurrence was defined as headache response at 2 hours with a return of moderate or severe pain over the next 24 hours. Patients taking 5 or 10 mg had higher response rates for treatment of recurrent pain compared to placebo but only the 10 mg group had a difference that was associated with a p value of < 0.05.

Figure 6: *Study 022, Two Hour Headache Response Rates*



Secondary outcome measures, pain free rate at 2 hours, change in associated symptoms (nausea, photophobia, phonophobia) were also in favor of drug when compared to placebo. Numerically, the differences were in favor of the 10 mg dose group.

For the treatment of a recurrent headache, patients were randomized to take either placebo or drug. The response rates for the recurrent headaches are summarized in the following table.

The response rates for the recurrent headaches in study 022							
Initial dose 5 mg				Initial dose 10 mg			
Recurrence treatment				Recurrence treatment			
5 mg		Plb		10 mg		Plb	
N	%	N	%	N	%	N	%
55	71	59	54	65	82*	75	44

*p value < 0.05 in comparison with placebo

Study 025:

This was a multicenter study evaluating the treatment of 4 individual migraine headaches. Patients were randomly assigned to one of 5 treatment sequences as summarized in Table 95 from Dr. Oliva's review. The number of patients assigned to each dose group is also included in this table. Doses taken for recurrent headaches were not randomized.

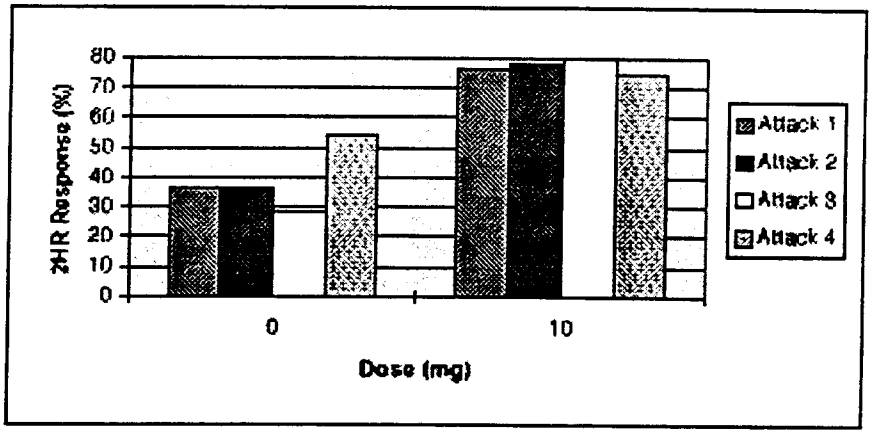
Table 95: Study 025, Treatment Assignment

Group (N)[1]	Attack 1	Attack 2	Attack 3	Attack 4
1 (83)	Placebo	10 mg	10 mg	10 mg
2 (82)	10 mg	Placebo	10 mg	10 mg
3 (84)	10 mg	10 mg	Placebo	10 mg
4 (77)	10 mg	10 mg	10 mg	Placebo
5 (81)	10 mg	10 mg	10 mg	10 mg

[1]Number of patients in group who treated at least the first attack

The primary analysis was confined to the treatment of the first headache. The 10 mg group had a significantly higher response rate at 2 hours compared to the placebo group. Similar results were seen for the secondary outcome measures, including associated symptoms. The patients taking 10 mg had consistently highef response rates compared to the placebo group for all 4 headaches. These results are summarized in figure 8 from Dr. Oliva's review. For the 50 patients who did not respond to the 10 mg dose with treatment of the initial headache, 35 responded with the 10 mg dose for their second attack. Of the 315 patients who treated 3 or 4 headaches only 12 did not respond to any treatment. Of the 252 patients who treated three attacks with 10 mg, 60% responded all three times.

Figure 8: Study 025, Two Hour Response Rates in Multiple Attacks (N=407)



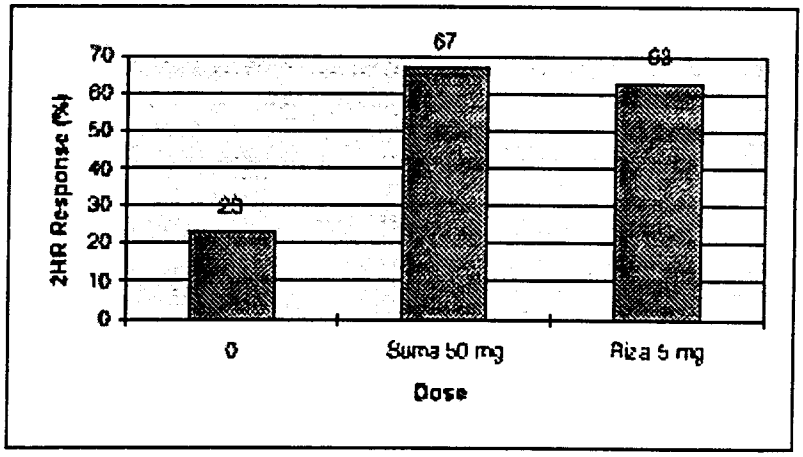
For the treatment of a recurrent headache, patients were randomized to take either placebo or drug. The response rates for the recurrent headaches are summarized in the following table.

The response rates for the recurrent headaches in study 025															
Attack 1				Attack 2				Attack 3				Attack 4			
10 mg		Plb		10 mg		Plb		10 mg		Plb		10 mg		Plb	
N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
96	72	11	46	91	86	13	77	94	85	7	86	77	90	15	60

Study 029:

This was a non US study with patients randomized to placebo, 5 mg of rizatriptan or 50 mg of sumatriptan in a 1:4.5:4.5 ratio. The primary outcome measure was the time to response within the first 2 hours. Patients treating a headache with placebo, 5 mg of rizatriptan and 50 mg of sumatriptan were 80, 352 and 356, respectively. Both active treatments were superior to placebo in the 2 hour response rate (see figure 9 from Dr. Oliva's review), associated symptoms, quality of life and satisfaction with medication. No statistically significant differences were noted between the active treatment groups for the primary outcome measure of time to response (p=0.514). The only differences between the active groups associated with a p value of < 0.05 was that rizatriptan had a better score at 2 hours for the presence of nausea (30 vs 37%) and that sumatriptan was superior to rizatriptan in pain response and pain free at 4 hours (81 vs 72% and 51 vs 42% , respectively).

Figure 9: Study 029, Two Hour Response Rates

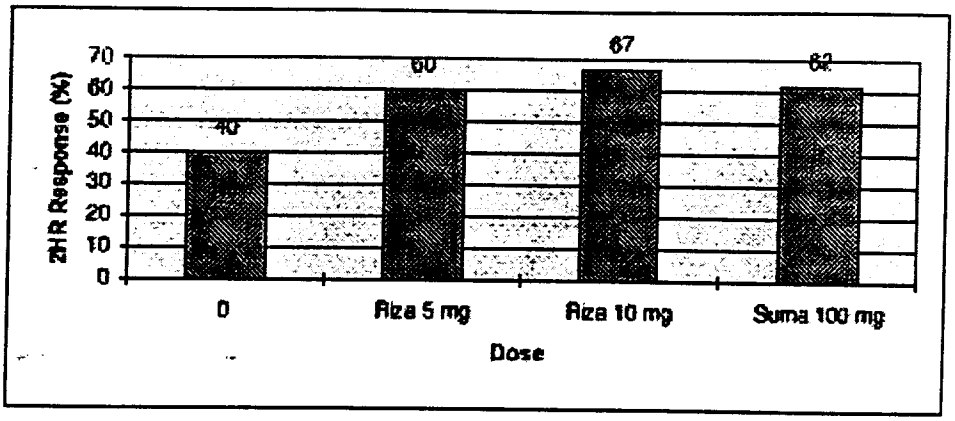


Study 030:

This was a non US study with patients randomized to placebo, 5 mg or 10 mg of rizatriptan or 100 mg of sumatriptan in a 1:1:2:2 ratio. Patients treating a headache with placebo, 5 mg, 10 mg of rizatriptan and 100 mg of sumatriptan were 159, 163, 386 and 383, respectively. The primary outcome measure was the time to response within the first 2 hours.

A comparison of the time to response and the response rates of placebo and each active treatment group 2 hours following treatment were associated with a p value of < 0.05. Similar results were seen for the associated symptoms and pain free rates. For the primary outcome measure, time to response, there was no statistically significant difference between the active treatment groups. Comparisons of response rates (see figure in table 52 from Dr. Oliva's review) and associated symptoms between the 5 and 10 mg rizatriptan and 100 mg sumatriptan groups were associated with p values > 0.05 except for the pain free rates at 2 hours and the presence of nausea at 2 hours which favored the 10 mg group over either the 5 mg group or the sumatriptan group. For the 10 mg group, the comparison of the functional disability rating, satisfaction with medication and work and social quality of life were also associated with a p value < 0.05 in a comparison with either 5 mg of rizatriptan or 100 mg of sumatriptan.

Table 52: Study 030, Two Hour Headache Response Rates (N=1099)



Additional sponsor analyses :

From an evaluation across studies, there did not appear to be a difference in effect related to sex or age of the patient . There was no difference in effect seen in women taking or not taking oral contraceptives. Patients with moderate headaches at baseline had higher response rates than patients with severe headaches at baseline [[.

In extensions to the efficacy studies, patients were randomized to 5 mg, 10 mg or "standard care" and assessed their pain following treatment. Overall, the sponsor noted that the response rates for the 10 mg group was higher than "standard care" (p value < 0.05) and numerically higher than the 5 mg group.

Additional reviewer analyses:

Time to initial response:

The time point when a patient first noted headache response (headache severity of mild or none). Patients without response within 2 hours were censored at 2 hours.

Time to remedication:

Remedication was defined as any escape medication or additional study medication following the initial treatment. Data from all trials was pooled. Patients without any additional treatments within 24 hours of the initial dose were censored at 24 hours.

Sponsor's conclusions

1. Rizatriptan doses of 5 to 40 mg are effective in the acute treatment of moderate or severe migraine attacks. The efficacy of rizatriptan is dose related. 2.5 mg is a no-effect dose, and 40 mg is the most effective dose studied.

2. Rizatriptan 5 mg and 10 mg possess the most favorable therapeutic ratios. Rizatriptan 10 mg is more effective than rizatriptan 5 mg.

3. Rizatriptan 5 mg and 10 mg are effective in treating both the headache and the non-headache aspects of a migraine attack, including associated migraine symptoms (nausea, vomiting, photophobia, and phonophobia) and functional disability. Patients taking rizatriptan 5 mg and 10 mg also have a reduced need for escape medication and had

improved quality of life in the 24 hours after dosing. [note: I do not agree that the sponsor has provided sufficient data to support the claims for improvement in functional disability and quality of life since the measures used to assess these claims have questionable validity]

4. Rizatriptan 5 mg and 10 mg are effective as early as 30 minutes after dosing. [Note: This statement is misleading. Patients given rizatriptan were noted to have headache response as early as the first assessment. the same is true for patients receiving placebo. The primary outcome measure was designed to assess the outcome 2 hours after treatment. For other migraine drugs, we have included a graph of the time to response to describe the results.]

5. The efficacy of rizatriptan 10 mg is maintained when it is used to treat multiple discrete migraine attacks; the majority of patients respond to most of the attacks treated. [This was found in the other drugs in this class]

6. Migraine headache recurs in approximately one third of patients who initially report relief following rizatriptan 5 mg and 10 mg. Both rizatriptan 5 mg and 10 mg are effective in treating headache recurrence. Rizatriptan increases the duration of relief (time to recurrence) in those patients who experience recurrence. [Note: We have used the time to remedication following initial treatment to illustrate the differences between groups.]

7. Rizatriptan 10 mg provides pain relief earlier than sumatriptan 100 mg. More patients are pain-free and have reduced functional disability following rizatriptan 10 mg than after sumatriptan 100 mg. Rizatriptan 5 mg and sumatriptan 50 mg show comparable overall efficacy through 2 hours after dosing. Fewer patients report nausea as an associated symptom following rizatriptan 5 mg and 10 mg than after sumatriptan 50 mg or 100 mg. [Note: The comparison studies did not use complete dose ranges of sumatriptan for a fair comparison. Even with this in mind, a comparison of the primary endpoint did not reveal any differences between the two active agents. In the three comparison studies, there were multiple secondary outcome measures. Some were in favor of rizatriptan and others were in favor of sumatriptan.]

8. Both rizatriptan 5 mg and 10 mg are highly effective when used long term for the acute treatment of intermittent migraine attacks occurring over a period of up to 1 year. Efficacy is consistent over the course of a year of treatment. Rizatriptan 10 mg is more effective than either rizatriptan 5 mg or standard care treatment. [Note: Efficacy results from an open label trial are of questionable validity.]

Reviewer's conclusions

The primary efficacy review was completed by Dr. Armando Oliva and he concluded that there was sufficient evidence for the efficacy of the drug for the acute treatment of migraines. See his review for details.

Team leader's conclusions

The sponsor has provided sufficient evidence for the efficacy of the drug for the acute treatment of migraines. The sponsor provided evidence from a total of 8 studies, of which 4 were adequate and well controlled studies that evaluated the formulation proposed for marketing.

In addition to the evaluation of the efficacy of a single dose for the acute treatment of a migraine provided in other NDAs for this indication., the sponsor has also compared the

efficacy with sumatriptan and have evaluated the efficacy of a second dose for headache recurrence.

As with other migraines NDAs, the patients enrolled were predominantly female and white with a mean age of about 40 years, ranging in age except for study 020 where 25 patients over the age of 65 (mean 68) were treated. Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed at 0.5, 1, 2, 3 and 4 hours after dosing. The primary outcome measure was headache response at 2 hours.

The results of the studies demonstrated that doses >=5 mg are effective for the acute treatment of migraine. Groups treated with doses from 5 to 40 mg had a statistically significant greater rate of headache response at 2 hours when compared to groups treated with placebo. The results from the studies are summarized in the following table.

Table: Response rates 2 hours following treatment of initial headache (n=number of patients)

Study	Placebo	2.5 mg	5 mg	10 mg	20 mg	40 mg	Sumatriptan[1]
004	33% (n=21)				50% (n=8)	75%* (n=36)	
008	18% (n=85)			52%* (n=89)	56%* (n=82)	67%*† (n=120)	46%* (n=72)
014	18% (n=67)	21% (n=75)	45%* (n=130)	48%* (n=145)			
020[2]	33% (n=38)			54% (n=99)			
022	35% (n=304)		62%* (n=458)	71%*# (n=456)			
025[3]	37% (n=82)			77%* (n=320)			
029	23% (n=80)		63%* (n=352)				67%* (n=356)
030	40% (n=159)		60%* (n=164)	67%* (n=385)			62%* (n=387)

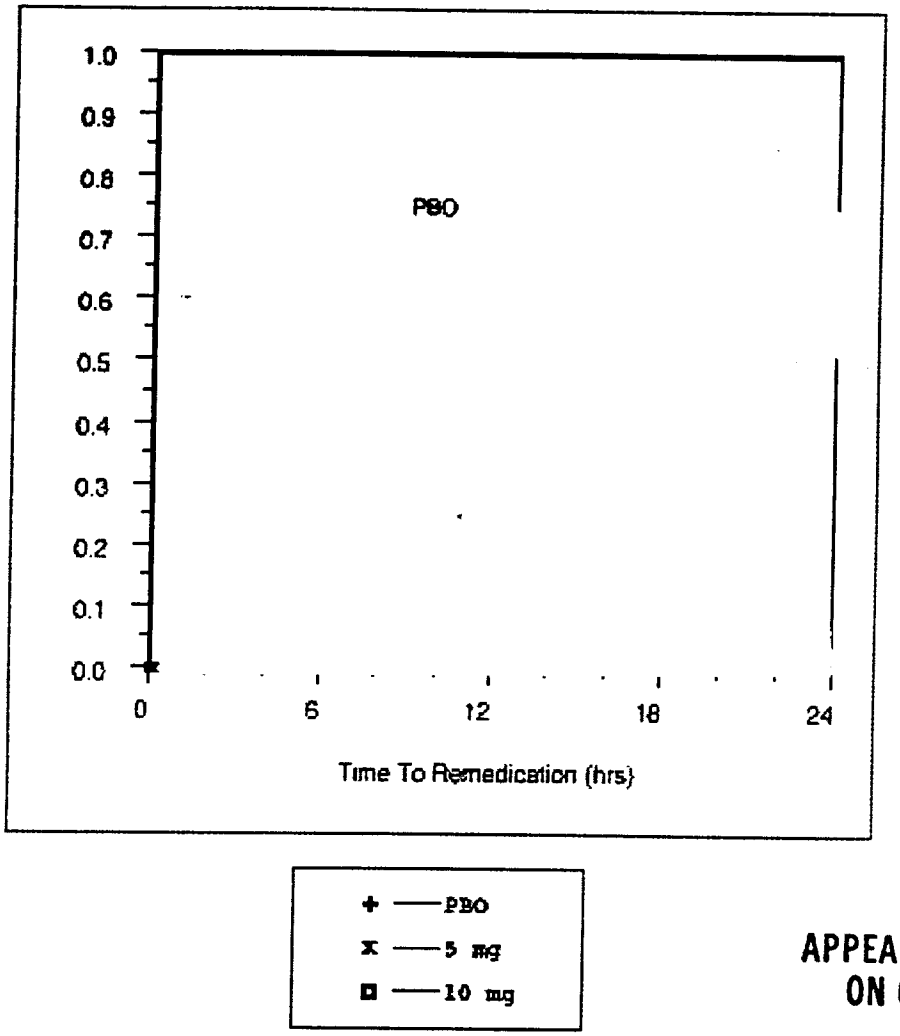
*p value < 0.05 in comparison with placebo
#p value < 0.05 in comparison with 5 mg
†p value < 0.05 in comparison with sumatriptan
[1]Sumatriptan dose was 100 mg in all studies except 029 where the dose was 50 mg.
[2]This was the only study in which patients treated the headache in a clinic setting (no statistical tests were reported)
[3]Results for initial headache only.

There is evidence that the response is dose related. In study 014, the response rate for the 2.5 mg dose was not different from placebo. In studies 004 and 008, doses of 40 mg had higher response rates compared to lower doses.

The sponsor considered doses above 10 mg to be less desirable because of a higher adverse event rates and only evaluated doses of 5 and 10 mg in phase 3. Between the 5 and 10 mg dose, a greater proportion of patients had headache response 2 hours following treatment and in one of three studies, the difference was associated with a nominal p value of < 0.05. The 10 mg dose was also numerically better than the 5 mg dose on the secondary outcome

measures including time to response and time to remedication. The latter finding is included in figure 13 from Dr. Oliva's review.

Figure 13: Estimated Probability of Remedication during the first 24 hours*



* pooled data from studies 022, 025 (first attack), 029, 030, revised data, 3/25/98

For patients with migraine associated photophobia, phonophobia and nausea at baseline, there was a decrease incidence of these symptoms in the patients receiving active treatment compared to those receiving placebo.

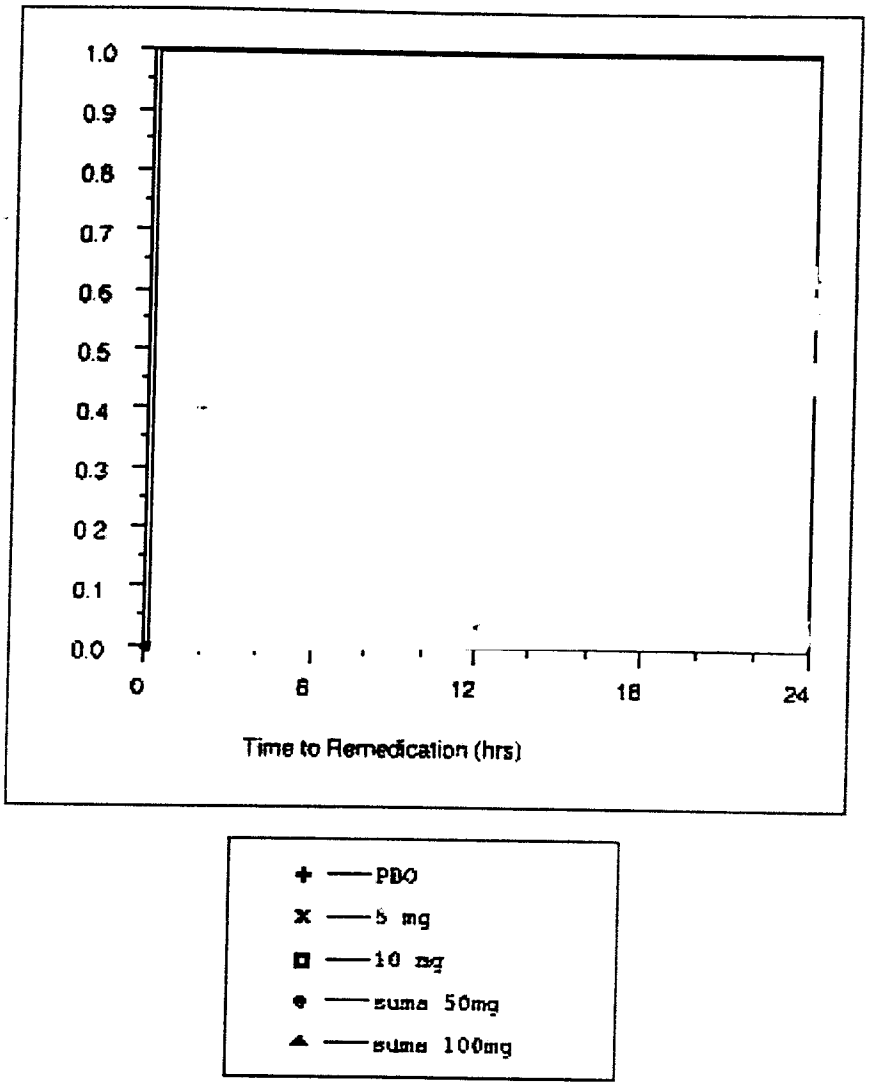
The sponsor also looked at the effect of a second dose taken for a recurrent headache in two studies (022 and 025) by randomly assigning placebo or drug as the treatment for a recurrent headache. The results are mixed in regards to the efficacy of the second dose. In study 022, the response rates for the active treatments were greater than those given placebo for a recurrent headache but only the comparison of the 10 mg group was associated with a p value < 0.05. In study 025, numerically, the response rates following the 10 mg dose was higher than following placebo but some of the differences were small. The sponsor elected not to formally analyze this data.

I recommend that the clinical section of labeling be similar to the labeling for recent migraine drugs in this class and contain the response rates at 2 hours for all studies and Kaplan Meier curves showing the time to headache response and time to remedication for the 4 outpatient studies that utilized the marketed formulation.

The dosing and administration section should also be similar to that used for recent migraine drugs. It should note that both the 5 and 10 mg dose is effective with a greater proportion of patients achieving headache response following the 10 mg dose compared to the 5 mg dose. It should be pointed out that higher doses are associated with greater adverse effects and are not recommended.

I do not feel that the sponsor has adequately demonstrated that their drug is superior to sumatriptan. First the comparison studies failed to use adequate dose ranges for comparisons. Doses of 25, 50 and 100 mg of sumatriptan should be compared directly to doses of 5 and 10 mg. Second, the studies did not demonstrate a statistically significant difference between drugs in the primary outcome measure. There were some secondary outcome measures that were numerically in favor of one or the other treatment but these differences could not be judged to be statistically significant after taking into account that the measures were chosen retrospectively and the comparisons were not adjusted for multiplicity. The similarity of the drugs is demonstrated in the response rates at 2 hours (see table above) and the time to remedication seen in figure 15 in Dr. Oliva's review.

Figure 15: Estimated Time to Remedication, Studies 029 and 030



* pooled data from studies 029, 030, revised data 3/25/98

Safety

Dr. Oliva reviewed the safety portion of the NDA and 120 day safety update. The cut off date for the NDA was 9/30/96 (serious adverse events had a cut off date of 2/28/97). The safety update included information up to 6/30/97 (serious AEs had a cut off date of 7/31/97).

APPEARS THIS WAY
ON ORIGINAL

Exposure

The sponsor's safety data base includes an adequate number of patients exposed to the drug.

Single doses: Approximately 300 healthy subjects and 3700 patients were exposed to at least one dose of the drug in 21 phase 1 studies and 10 phase 2/3 studies, respectively. The sponsor plans on marketing the drug at doses of 5 or 10 mg. The number of patients in the phase 2/3 trials receiving doses of 5, 10 or > 10 mg of the drug are 1165, 1180 and 492, respectively.

Repeated doses for a single headache: For the approximately 2,000 attacks treated in the controlled trials with 10 mg, 80% were treated with a single dose, 13% were treated with 2 doses and 7% were treated with three doses (about 140 patients). An additional 24 patients took 3 doses of 5 mg to treat a single headache. In the long term extension studies about 15% of the attacks were treated with three doses of drug.

Long term treatment: The number of patients taking rizatriptan about 4 times a month, on average, long term is summarized in the following table.

Long term exposure: treatment of = 2 headaches per month on average.		
	5 mg	10 mg
>= 6 months	347	496
>=12 months	114	157

Deaths and Serious AEs

APPEARS THIS WAY
ON ORIGINAL

There were no deaths reported.

In the phase 1 studies, serious AEs were reported in 4 of the 313 subjects on drug compared to 1 of the 134 exposed to placebo. Two of the subjects received a single 80 mg dose. These patients had a syncopal episode associated with bradycardia and hypotension which occurred with venipuncture. The other serious AEs were elective abortion and irritable bowel syndrome.

In the phase 2 studies, one patient out of 974 experienced a serious adverse event. this was a 26 year old male patients enrolled in the cardiac monitoring study (020). He was assigned to 10 mg for the treatment of a severe headache. Approximately 90 minutes following treatment, the patient developed mild chest pain with palpitations. An ECG showed a normal sinus rhythm with moderate right axis deviation and nonspecific T wave abnormalities. He was treated with oxygen and the pain subsided over a few minutes. He developed a brief (1 minute) episode of tachycardia 2 hours following dosing. The patient subsequently experienced episodes of chest pain over the next 2 hours including severe pain associated with tachycardia. The last episode of pain was treated with nitroglycerin

with relief. Isoenzymes were normal. With the severe pain, there was a mild increase in diastolic pressure. ECGs prior to the start of the chest pain were normal. A cardiology consult noted that the ECGs were consistent with myocardial ischemia. . A subsequent stress test was normal.

In the phase 3 studies, one patient had a syncopal spell after taking a total of 15 mg. The patients had a history of syncope with her migraines which are associated with nausea and vomiting.

Other serious adverse events of note include an episode of abdominal pain, pulmonary embolism, agranulocytosis, thrombocytopenia, asthma. In the cases of thrombocytopenia and agranulocytosis, the patients were on other medications, diflunisal and Bactrim, respectively. These other drugs were implicated as causing the hematological disorders from results of in vitro testing including the discovery of antibodies to the other drugs. A 45 year old female patient had an episode of pulmonary embolism 5 days after treating her 11th migraine with 10 mg over a period of 105 days. No causes of the embolism was found. A 40 year old female had chest pain following treatment of her 14th migraine with 10 mg of rizatriptan over a 4 months period. The pain was unrelieved by nitroglycerin and was similar to episodes that occurred without any treatments. An ECG showed clockwise rotation and non specific ST-T wave changes. Cardiac enzymes and a stress test was normal.

Dropouts

The rates for discontinuation from the controlled clinical trials is confounded by the short duration of the trials. In the long term extension studies, 4% of patients using rizatriptan discontinued from the study because of adverse events. This included 25 of the 700 patients treating headaches with 5 mg and 36 of the 825 patients treating headaches with 10 mg. The most common causes for discontinuation included nausea, dizziness, chest pain, somnolence, rash, increased blood pressure and atypical sensations. All of these events occurred in = 1% of patients.

Adverse events

The most common adverse events are summarized in the following table. The symptoms seen in the randomized controlled trials were similar to those seen in the long term extensions studies and included dizziness, nausea, somnolence, fatigue, chest pain, vomiting, diarrhea, headache, paresthesia and pharyngeal discomfort. As with other migraine drugs, the sponsor should combine the atypical symptoms and the pain, tightness and pressure sensations together.

Adverse event incidence in the phase 3 studies after 1, 2 or 3 doses												
	5 mg				10 mg				Placebo			
Number of Doses	1	2	3	Any	1	2	3	Any	1	2	3	Any
Total Patients	144	54	24	222	337	142	73	552	65	14	4	83
% with any AE	32	37	33	**33**	43	55	51	**47**	23	50	25	**28**
Dizziness	4	6	0	**4**	9	11	7	**9**	5	14	0	**6**
Somnolence	5	4	0	**4**	9	10	12	**10**	3	14	0	**5**
Nausea	8	4	8	**7**	6	11	7	**7**	3	7	0	**4**
Asthenia/ fatigue	1	2	0	**1**	6	11	6	**7**	0	7	0	**1**
Pain, chest	2	2	4	**2**	4	4	4	**4**	2	0	0	**1**
Paresthesia	4	2	0	**3**	4	6	4	**4**	0	0	0	**0**
Headache	1	4	0	**2**	3	4	1	**3**	0	7	0	**1**
Dry mouth	5	2	4	**4**	3	5	7	**4**	0	7	0	**1**
Hypesthesia	0	2	0	**<1**	2	<1	0	**1**	2	0	0	**1**
Vomiting	4	2	0	**3**	2	2	8	**3**	2	7	0	**2**
Tachycardia	0	0	0	**0**	2	0	3	**1**	0	0	0	**0**
Tightness, regional	1	0	0	**<1**	2	<1	1	**1**	0	0	0	**0**
URI	1	0	4	**1**	2	3	0	**2**	3	0	0	**2**
Pain, abdominal	3	4	0	**3**	2	1	3	**2**	0	0	0	**0**
Mental acuity dec.	0	0	0	**0**	2	1	3	**2**	3	0	0	**2**
Euphoria	0	0	0	**0**	1	<1	0	**<1**	0	0	0	**0**
Dyspnea	0	0	4	**<1**	1	1	0	**1**	0	0	0	**0**
Flushing	<1	2	0	**<1**	1	1	3	**1**	2	0	0	**1**

APPEARS THIS WAY
ON ORIGINAL

Lab testing

No lab abnormalities occurring in the phase 3 controlled studies were rated as serious or led to discontinuation of treatment. There did not appear to be any lab abnormalities associated with the use of the drug.

APPEARS THIS WAY
ON ORIGINAL

Vital signs and ECGs

In a clinical pharmacology study, increases in diastolic BP of a maximum of 4.7 mmHg was seen in healthy subjects given 10 mg every 2 hours times three doses. In a clinical pharmacology study, 12 patients received doses of 80 mg over 2 hours. 3 hours after the first dose, one 29 year old female developed bradycardia, vomiting and dizziness. The bradycardia was associated with a 10 second period of AV dissociation which responded to atropine. A 25 year old male in the same study developed dizziness, syncope and a 5 second systolic pause after a painful venipuncture two hours after dosing with 80 mg. the 80 mg was given over 4 hours. The drug did not appear to led to any other clinically significant changes in blood pressure or heart rate.

A single study was performed in patients where ECGs were taken at regular intervals (Study 020). Aside from the single patient with chest pain and ECG changes described in the serious AE section, no significant ECG changes suggestive of ischemia were noted.

Other

No specific interaction between concomitant medications (preventive treatments, oral contraceptives). The sex and age of the patients did not appear to effect the adverse event

profile. Only 21 patients = 65 were treated. The adverse event profile was similar for white and non white patients though differences related to race was difficult to assess because of the low enrollment of non white patients.

Reviewer's conclusions

Dr. Oliva concluded that based on the safety data presented,
1. Rizatriptan 5 mg or 10 mg is generally well tolerated.
2. The most common AE's were dizziness, somnolence, asthenia/fatigue, nausea, chest pain, vomiting, diarrhea, headache, paresthesias, and pharyngeal discomfort. These are typical of AE's seen with other 5HT1B/1D agonists.
3. Rizatriptan does not exhibit systematic ECG or laboratory abnormalities.
4. Diastolic blood pressure increases only slightly with rizatriptan use.
5. There are no clinically meaningful differences in the safety profile with regard to age, race or gender. Women generally have more AE's compared to men, but this was also present in placebo patients.
6. The safety profile of rizatriptan is not affected by medications concomitantly used for migraine prophylaxis, although rizatriptan levels are increased when used with propranolol. Lower doses of Maxalt should be taken when used concomitantly with propranolol.

Team Leader's conclusions

The sponsor has provided an adequate safety data base to support the proposed doses of 5 and 10 mg given up to three times per headache for the treatment of, on average, 4 headaches per month.

Rizatriptan appears to have a similar safety profile to other 5 HT1 agonists. There was one episode of chest pain associated with ECG changes suggestive of ischemic changes, there was evidence to suggest that the drug may lead to an increase in blood pressure and it is associated with "typical" adverse events such as sensations of pressure and tightness.

Compliance

During the inspection of the studies, the Division of Scientific Investigation (DSI) noted that center 011 in study 022 had the following violations: incomplete case report forms, did not report an adverse event, inadequate records for disposition of drug supplies, misleading statements in the patient recruitment brochure. DSI recommended that the investigator submit plans on how they will improve their center so that the events will not recur.

This site enrolled 33 patients in the 1218 patient study. The results from this center do not change the conclusions about the efficacy or safety of the drug.

Recommendations

The sponsor has provided evidence from more than one adequate and well controlled study that the drug is effective for the acute treatment of migraine headaches. The sponsor has also provided adequate safety data for the evaluation of the short term and long term safety of the drug. This evidence suggests that the drug is as safe as other drugs in its class that are currently marketed for this indication.

The attached labeling is consistent with labeling for other drugs in this class. The package insert for the Maxalt tablet and Maxalt MLT orally disintegrating tablet (formally Maxalt Rapidisc rapidly disintegrating tablet) will be the same. A single patient package insert will be used and will include special instructions for the use of the orally disintegrating tablet.

The sponsor is agreeable to the labeling except for three parts related to preclinical issues. First, the sponsor wants the drug classified as category B in regards to the safety for use of Maxalt during pregnancy and our reviewers feel that the drug should be category C. There does not appear to be a significant dispute with the findings of the reproductive toxicity studies. There was a reduction in weight in the offspring that occurred in the absence of maternal toxicity. The sponsor feels that the weight loss was transient but our reviewers note that the reduction in weight gain was seen both pre and post weaning. There is a dispute on the adequacy of the dose used in the studies. The sponsor feels that a dose 3.2 to 32 times the maximum recommended dose in humans is adequate. Our reviewers feel that since there are differences in the way that the drug is handled between species that dose, in itself, is not adequate to determine the proper dose. The dose is better determined by the presence of maternal toxicity which is a better indicator of drug effect than the magnitude of the dose used in humans. (It should be noted that the dose of 100 mg/kg/day was minimally toxic in other studies). The findings for Maxalt do suggest that the drug may have less fetal toxicity than seen with other drugs in this class, but the full spectrum of the developmental toxicity of the drug is not known since the developmental and reproductive toxicity studies did not use higher doses. In a dose finding study where higher doses were used (>=250 mg/kg/day), there was an increase in pup mortality rates. In the confines of the current classification system, I agree with our reviewer's recommendations that the category C is justified because of the finding of decreased weight, the suggested toxicity at higher doses and the lack of evaluation at adequately high doses.

Second, the sponsor wanted to describe two developmental toxicity studies. We included only one study because the second study involved a degradant.

Third, the sponsor wants to include results from albino rat and mouse study to address a potential concern for eye damage because the drug binds to melanin. These studies are not relevant to the problem since these animals do not have melanin. Other sponsors performed studies in pigmented animals.

There are no other outstanding issues.

I recommend that the drug be approved with the attached labeling.

APPEARS THIS WAY
ON ORIGINAL

/S/

Randy Levin, M.D.
Neurology Team Leader
rl/June 9, 1998