Cross-Discipline Team Leader Review

Date	9/9/2011
From	Eric Bastings
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	20,865 020
Applicant	Merck Co.
Date of Submission	3/25/2011
PDUFA Goal Date	9/25/2011
Proprietary Name / Established (USAN) names	Maxalt MLT (rizatriptan benzoate)
Dosage forms / Strength	Oral Disintegrating Tablet
Proposed Indication(s)	Acute treatment of migraine in pediatric patients age 12-17 years
Recommended:	Approval

1. Introduction

This sNDA was submitted in response to a 1/13/2010 amended Written Request for Maxalt MLT. Maxalt is a 5-$HT_{1B/1D}$ receptor agonist (triptan) indicated for the acute treatment of migraine in adults. The sponsor is requesting a new indication for the acute treatment of migraine in patients from 12 through 17 years of age.

The review team included the following members:
Clinical Pharmacology: Xinning Yang, Ph.D. (team leader: Angela Men, M.D., Ph.D.)
Clinical: Nushin Todd, MD.
Statistics: Xiang Ling, Ph.D. (team leader: Kun Jin, Ph.D; director: James Hung, Ph.D.).
Patient Labeling (DRISK): CDR Shawna Hutchins.
Labeling (SEALD): Jun Yan, Pharm.D.
Labeling (DDMAC): Quynh-Van Tran and Meeta Patel.

2. Background

Rizatriptan oral tablet (NDA 20,864) and orally disintegrating tablet (NDA 20,865) are both approved for the treatment of acute migraine in adults, at dose levels of 5 mg and 10 mg.

Prior to conducting the studies requested under this Written Request, the sponsor conducted two failed pediatric efficacy trials (#054 and #059) with the 5 mg tablet. The sponsor submitted the results of Study 054 (and of supporting PK Study 058) in a 10/27/99 labeling supplement to NDA 20-864 (SE5-02), and shortly before that (on 10/7/1999) sent a proposed pediatric study request (PPSR) to the division, proposing to conduct additional migraine studies. Study 054 evaluated the short-term safety and efficacy of Maxalt 5 mg in adolescent migraineurs age 12-17 years. As noted by Dr. Armando Oliva in an 11/24/2000 memorandum (filed to the rizatriptan IND 40,458), the results of the Study 054 were negative. Dr. Oliva discusses that as a result of this finding, the division decided at the time not to ask for any additional studies [under a Written Request]. The division informed the sponsor of that decision in a 4/17/2000 telecon. During that telecon, the sponsor informed the division that they were planning to conduct a second efficacy study which, they believed, would demonstrate efficacy (protocol #059 submitted to IND 40,458 Serial Number 215, dated 3/21/2000). The division responded that, although the division was not requesting any additional pediatric studies at that time, should the results of that second study demonstrate efficacy, the division would revisit its position and would consider issuing a Written Request for a long-term safety study. The PPSR was formally declined by the division in a 1/22/01 letter.

The sponsor sent a second proposed pediatric study request on 11/10/2001. The division also declined issuing a Written request at that time, because the interim analysis of the second adolescent study of rizatriptan for migraine was negative.

Merck sent a third proposed pediatric study request on 10/25/2007. In that request, the sponsor argued that the failure of prior trials may be due to inadequate exposure of rizatriptan especially in heavier subjects, and proposed to conduct a new efficacy study. In the interim, the division had also gained experience from a number of failed pediatric migraine studies, and had identified that the high placebo response and short duration of migraine attacks in the pediatric population were two likely contributors to the failure of prior trials. The division has been encouraging sponsors to submit pediatric trial proposals using enrichment procedures, such as randomizing only patients who did not have an early response to a placebo challenge, and/or patients with a history of relatively long (e.g. >3-4 hours) migraine attacks. In that context, the division issued a Written Request on 3/6/2009. This Written Request asked for a PK/safety study, a short-term safety and efficacy study, and a long-term efficacy study in pediatric patients age 6-17 years.

On 8/26/2009, the sponsor requested the Written Request to be amended, by limiting the studies to patients age 12-17 years. The rationale for that request was that recruiting patients in the younger age group (i.e., 6-11 years of age) was posing significant operational challenges, making it not feasible to complete the pediatric program within the Agency-specified timelines. Instead, Merck proposed enrolling patients aged 12-17 years, and submitting a plan to study the 6-11 year old population for Agency review and concurrence by March 2011 (but outside of the context of a Written Request). The division found the argument compelling, and (in consultation with PeRC) issued an amended Written Request on 1/03/2010. The amended Written Request listed the following studies:

Study 1: To assess the safety and tolerability of single doses of rizatriptan benzoate, and evaluate the pharmacokinetics of rizatriptan benzoate in pediatric migraineurs 12 to 17 years of age, compared to adults (historical controls).

Study 2: To evaluate the efficacy and safety of rizatriptan benzoate in the treatment of pediatric patients age 12 to 17 years of age with a history of migraine headaches.

Study 3: To evaluate the long-term safety of rizatriptan benzoate in the treatment of pediatric patients 12 to 17 years of age with a history of migraine headaches.

3. CMC/Device

N/A.

4. Nonclinical Pharmacology/Toxicology

No nonclinical study was required to support clinical trials in the adolescent pediatric population.

5. Clinical Pharmacology/Biopharmaceutics

Xinning Yang, Ph.D., conducted the clinical pharmacology review. Dr. Yang notes that the sponsor submitted the results of a single dose PK study (#083) in the adolescent migraine population with the Maxalt MLT formulation, and in addition submitted data from two pediatric PK studies previously conducted with the tablet formulation (#048 and #062).

Dr. Yang finds the sNDA acceptable from a Clinical Pharmacology perspective, and believes that the sponsor has fulfilled the requirements described in the 1/13/2010 Pediatric Written Request.

Dr. Yang notes that the AUC and Cmax of rizatriptan after a single dose of Maxalt-MLT are lower in heavier pediatric patients, supporting the use of a higher dose in heavier patients to achieve the same level of exposure as lower weight patients. Dr. Yang believes that the Maxalt PK studies provide support for the sponsor's plan to evaluate a 10 mg dose of Maxalt in patients ≥ 40kg, and a 5 mg dose in patients < 40kg. Using that approach, both weight groups achieve a Cmax similar to that of adults receiving a 10 mg dose of Maxalt-MLT (based on a historical comparison). Dr. Yang also notes small differences in AUC between adults and the pediatric population (17% higher in pediatric patients ≥ 40kg than in adults, and 15% lower in pediatric patients <40kg than in adults). As discussed by Dr. Yang, Cmax is most relevant for that indication, so that the differences in AUC have minimal clinical significance.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

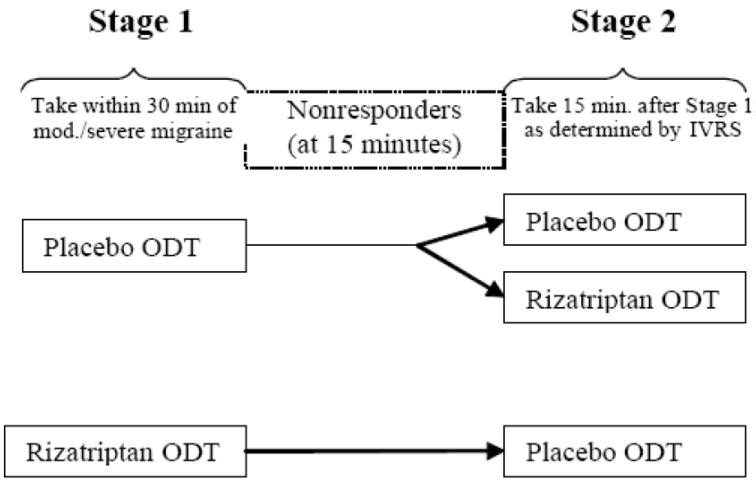
As discussed above, two previous trials (#054 and #059) with rizatriptan 5 mg in adolescents aged 12 to 17 years failed to demonstrate a significant treatment effect. The sponsor attributed that failure to insufficient patient exposure with the 5 mg dose in older and heavier children, and to a high placebo response rate in the pediatric population. The division found that argument reasonable, which supported the conduct of a new appropriately designed study to address these two issues.

The new efficacy study (#082) was randomized, double-blind, placebo-controlled, parallel group, and used a body weight-based dosing, intended to match the exposure of 10 mg rizatriptan in adults. Patients ≥40 kg received Maxalt-MLT 10 mg ODT or placebo, while patients <40 kg received Maxalt-MLT 5 mg ODT or placebo. The study had an elaborated enrichment design, by excluding placebo responders prior to randomization. In addition, the trial was conducted in patients who had not achieved a satisfactory response with prior acetaminophen or NSAID treatment. Arguably, selecting patients with no prior response to analgesics may have made it more difficult to achieve success, as that population may have

been more refractory to acute treatments of migraine in general (including triptans), but it also makes the trials results more relevant.

As discussed by Dr. Ling, who conducted the statistical review, a two-stage double-randomization design was used to attempt to exclude placebo responders (Figure 1):

Figure 1: Study design (copied from Figure 1 of Dr. Ling's review)



Stage 1
Stage 1 was designed to identify and exclude placebo responders from the primary analysis. Patients were randomized in 20:1 ratio to placebo or rizatriptan to treat a single migraine attack of moderate or severe intensity (patients randomized to rizatriptan during stage 1 were not re-randomized in stage 2, and were not part of the primary analysis). After 15 minutes, patients who reported mild or no pain (i.e., responders) were instructed to take no further study medication. Patients who reported continued moderate or severe pain (i.e., non-responders) were moved to Stage 2.

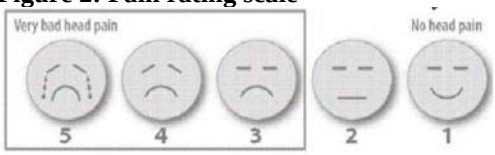
Stage 2
During Stage 2, non-responders who received placebo in Stage 1 were randomized in a 1:1 ratio to rizatriptan or placebo, with a stratified randomization based on age (6 to 11 years old vs. 12 to 17 years old) and migraine intensity reported at 15 minutes post Stage 1 dose (moderate vs. severe), which was used as the Stage 2 baseline pain severity. Non-responders who received rizatriptan in Stage 1 were allocated to receive placebo in Stage 2, and were not part of the primary analysis.

The primary analysis of efficacy data only included patients who did not respond to placebo at Stage 1 and were randomized in Stage 2.

The primary efficacy endpoint was pain freedom at 2 hours post Stage 2 dosing. Pain intensity was assessed using a five-face pain scale with migraine pain intensity defined as follows: face 1 = no pain; face 2 = mild pain; face 3 to 4 = moderate pain; face 5 = severe pain (Figure 2).

Pain freedom was defined as a reduction in headache severity from Face 5/4/3 at Stage 2 baseline to face 1.

Figure 2: Pain rating scale



Pain relief at 2 hours (defined as a reduction in headache severity from Face 5/4/3 at Stage 2 baseline to Face 2/1) was a secondary efficacy endpoint.

Exploratory Measures included:
• Absence of Photophobia at 2 hours
• Absence of Phonophobia at 2 hours
• Absence of Nausea at 2 hours
• Sustained Pain Freedom from 2-24 hours and from 2-48 hours.

A logistic regression model was used to compare the treatment groups with respect to pain freedom at 2 hours post-dose. Factors in the model included treatment group (rizatriptan vs. placebo), Stage 2 baseline headache severity (moderate or severe), and region (US or ex-US).

A total of 1010 subjects were randomized at 134 sites in the United States and 57 sites internationally, with 702 patients treating with study medication at stage 1. Dr. Ling observes that of the 702 treated patients, 61% were female, 65% were white, 73% were from the US, 17% were from the EU, 48% were 12 to 14 years of age, and 52% were 15 to 17 years of age. As the median body weight for 12 yr children is 40-42 kg, not surprisingly, most patients in the study (over 90%) were randomized to a 10 mg dose or placebo. Among patients who used treatment at either stage, few discontinued (7.3%), and mostly for protocol violations.

Half of the patients had typical duration of untreated migraine attacks of 2-6 hours, 37% had attacks lasting 7-24 hours, and 13% had migraine attacks usually lasting greater than 24 hours. The population was mostly (81%) triptan naïve, and most patients (81%) were not on migraine prophylaxis.

A total of 579 patients treated with study medication at stage 2, of which 570 had evaluable data. At the time of stage 2 treatment, 83.5% reported moderate headaches and 16.5% reported severe headaches at baseline. Most patients (77-79%) reported photophobia and phonophobia at baseline, while only 40% reported nausea.

The pain freedom rate at 2 hours (primary endpoint) was significantly greater for rizatriptan than for placebo (31% vs. 22%, p=0.025). Pain-relief at 2 hours trended in favor of rizatriptan (59% vs. 51%), but did not reach significance (p=0.080). The rate of nausea-freedom was nominally greater for rizatriptan than for placebo (87% vs. 78%, p=0.013), while the rates of photophobia-freedom (59% vs. 53%, p=0.257) and phonophobia-freedom (64% vs. 57%, p=0.111) were numerically in favor of rizatriptan.

Dr. Ling notes that the treatment effect in pain freedom and pain relief response was consistent across subgroups divided based on age, gender, race and region. There were differences, however, between the body weight-based subgroups (Table 1). In patients with a weight <40 kg (who were to receive a 5 mg dose of rizatriptan), the rate of pain-freedom was numerically greater for placebo (38%) than for rizatriptan (35%). The rizatriptan response rate, however, was numerically greater in patients with a weight <40 kg (35%) than in patients with a weight of ≥40 kg (30%). The main apparent difference was a markedly higher placebo-response in patients < 40kg (38.1%), compared to patients weighting ≥40 kg (21%). As discussed above, the <40 kg subgroup was very small (less than 10% of the study population), so that the elevated placebo rate in that subgroup may represent a chance finding, or may be related to a higher placebo response in patients <40 kg (who were generally younger than heavier patients).

Table 1: Number of patients reporting Pain Freedom at 2 hours Post Stage 2 Dose, by weight subgroup (copied from Table 2 of Dr. Yang's review)

Subgroup	Rizatriptan (N=285)		Placebo (N=289)	
	n/m	(%)	n/m	(%)
Baseline Weight				
< 40 kg	9/ 26	34.6	8/ 21	38.1
≥ 40 kg	78/258	30.2	55/265	20.8

As the rizatriptan tablet is bioequivalent to the orally disintegrating tablet, I believe that the efficacy of the rizatriptan tablet in the adolescent population can reasonably be extrapolated from Study 082, which used the orally disintegrating tablet.

8. Safety

As discussed by Dr. Todd, there was no major difference in the rizatriptan safety profile in the adolescent population compared to the adult population.

The long-term safety database included in this supplement is acceptable, as by the time of the 120-day safety update, out of 606 patients enrolled, 499 patients had completed at least 6 months of treatment, and 432 had completed at least 12 months of treatment. The exposure well exceeded the typical division's requirement for the size of the pediatric migraine safety database[1], as by the 120-day safety update, 423 patients had treated at least one migraine per month, on average, for a 6-month duration, and 339 patients had treated at least one migraine per month, on average, for a 12-month duration.

There was on death (motor vehicle accident), and 20 serious adverse events (SAEs) in the development program at the time of submission of the NDA (and 25 SAEs by the time of the 120-day safety update). Dr. Todd reviewed the cases, and concluded that no event appear

[1] At least 300 patients treating an average of at least 1 migraine attack per month for 6 months, and at least 100 patients treating an average of at least 1 migraine attack per month for 12 months

related to rizatriptan, with the exception of 4 cases of overdose (defined very conservatively as taking a second dose within 24 hours), which had no significant clinical consequence.

Two patients experienced suicidal ideation (0.3%), and three patients (0.5%) attempted suicide. None of these five events was considered to be drug-related by the sponsor or the investigator; two of these patients continued study medication and the three others were discontinued from the study due to these events. The suicide attempts took place 2 days, 6 days, and 9 days after the last dose of Maxalt, while the suicidal ideation events occurred 3 and 8 days after the last dose of Maxalt. Two of the patients who attempted suicide, and one of the patients who experienced suicidal ideation had a history of depression. The sponsor argues that given the background prevalence of suicidal ideation in adolescents (16% for those with migraine, and approximately 24% for those with migraine with aura), and the lifetime prevalence of suicide attempts among adolescents (9.7%), it seems unlikely that rizatriptan therapy was a contributing factor. While the open-label nature of the long-term study makes it impossible to make definite conclusions, I find the sponsor's argument reasonably persuasive.

There were no dropouts in the single-dose efficacy study related to an adverse event. In the long-term safety study (and by the time of the 120-day safety update), a total of 30% of patients discontinued, with few discontinuations because of an adverse event (14/606; 2.3%). Another 58 patients (10%) discontinued because of "withdrawal of consent". Some of these patients probably also discontinued because of an adverse event, but considering the overall safety profile, no further investigation is in my opinion needed regarding the actual reason for withdrawal.

The proportion of patients with common adverse events in the controlled trial was similar on drug (24%) and on placebo (23%). There were few events on Maxalt with an incidence ≥ 2% and greater than placebo (Table 2), and the differences between drug and placebo were small (under 1%).

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

	% of Patients	
Adverse Experiences	MAXALT-MLT (n=337)	Placebo (n=365)
Gastrointestinal disorders	6.8	7.9
Nausea	3.0	2.7
General disorders and administration site conditions	4.2	4.4
Fatigue	2.4	2.2
Nervous system disorders	7.7	6.8
Somnolence	3.3	2.5

Dr. Todd noted no clinically meaningful drug-related changes in laboratory values, vital signs, or EKGs in studies conducted with Maxalt MLT. Dr. Todd also reviewed older studies conducted with the tablet formulation, and noted one case of elevated ST segment that was reported as possibly related to rizatriptan in a long term safety study, but was noted 18 days after the last dose, which makes the drug causality unlikely. The overall profile of EKG evaluations does not suggest any worrisome pattern of abnormalities.

The sponsor also evaluated the post-marketing database of reported serious adverse events with pediatric use of rizatriptan, and notes no new safety signals in the pediatric population. I agree with that conclusion.

9. Advisory Committee Meeting

N/A.

10. Pediatrics

A review by the Pediatric exclusivity board review is pending. The review team believes that the terms of the Written Request have been met.

11. Other Relevant Regulatory Issues

None.

12. Labeling

This application triggered a PLR conversion. A multidisciplinary labeling review took place during the review cycle. Labeling is being discussed with the sponsor.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend approval.

Risk Benefit Assessment

This sNDA provides substantial evidence of safety and effectiveness of Maxalt for the adolescent population age 12-17 years. The studies submitted provide clear evidence of efficacy, based on a significant effect on the 2-hour pain free rate. No new safety finding of concern was identified in the adolescent population.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

Recommended Comments to Applicant

None.

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/s/

ERIC P BASTINGS
09/12/2011