Date	12/9/2011
From	Eric Bastings
Subject	Cross-Discipline Team Leader Review - Addendum
NDA/BLA # **Supplement#**	20,865 020
Applicant	Merck Co.
Date of Submission	3/25/2011
PDUFA Goal Date	12/25/2011
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 6-17 years
Recommended:	Approval

I refer the reader to my original CDTL memorandum, in which I commented on the safety and efficacy of Maxalt in adolescents age 12-17 years, and recommended approval for that new population. As described in my original memorandum, the original sNDA consisted of the results of 3 studies:

- Study 083 (PK study in patients age 6-17 years)
- Study 082 (safety and efficacy study in patients age 12-17 years)
- Study 086 (long-term safety study in patients age 12-17 years).

I also discussed in my memorandum that the original plan was for the sponsor to send a supplement for patients age 6-17 years, but because of operational challenges, an agreement was reached for the supplement to only include data for patients age 12-17 years, with investigations in younger patients to be submitted at a later time. For that reason, the primary analysis of safety and efficacy of Study 082 was modified to only include patients age 12-17 years, even though the study was actually conducted in patients age 6-17 years.

With the 120-day safety update, the sponsor provided a final report for Study 082 that included the younger age group (i.e., patients age 6-11 years). As the splitting of the study was made for the sole reason of meeting the deadline of the Written Request, and the final study report included a substantial subgroup of patients age 6-11 years, I believe it is appropriate to consider the results of Study 082 for the entire age range of 6-17 years, and use the pain-free rate in the combined age groups as the primary analysis for that study (and not as a secondary endpoint).

As described in the clinical and statistical review addenda, the pain-free rate (in patients age 6-17 years) was significantly greater for Maxalt than for placebo (33% vs. 24%; p=0.01). As described in Table 1, the pain-free rate was consistent between patients age 12-17 years and patients age 6-11 years, with an effect size of about 10% in favor of Maxalt. The study was not powered to show statistical significance in the subgroup 6-11 years, and the nominal p values must be interpreted with that in mind. It must also be noted that the placebo response was greater in the younger patients.

Table 1: Pain-free rate results in Study 082 (adapted from table 5, page 8 of the statistical review addendum)

Pain-free rate	Rizatriptan	Placebo	Nominal p-Value
6-17 years	126/382 (33%)	94/388 (24%)	0.010
12-17 years	87/284 (31%)	63/286 (22%)	0.025
6-11 years	39/98 (40%)	31/102 (30%)	0.269

Pain relief rate, a secondary endpoint, did not reach nominal p values under 0.05 in any of the age subgroups. It trended in favor of Maxalt in adolescents, but was similar in both treatment groups for patients age 6-11 years. A possible explanation to this discrepancy is that younger patients may have a greater difficulty in assessing pain intensity, and differentiating between mild and moderate pain. The migraine community has endorsed pain-free as a more relevant and preferred outcome in the adult population. I strongly support that view, and believe the pain-free rate should also be preferred in the pediatric population. Overall, I conclude that efficacy was established for patients age 6-17 years.

I described safety results in patients age 12-17 years in my original memorandum. The 120-day safety update includes short-term safety results in the 6-11 years age subgroup from Study 082, and updates the safety results to reflect the overall study population, i.e., patients age 6-17 years. Adverse events in the 6-11 years old subgroup, and in the overall population had a similar incidence for Maxalt and for placebo, with no adverse event having an incidence ≥1% greater on drug than on placebo. There was no serious adverse event attributed to Maxalt. I also commented in my original memorandum that no finding of concern was identified in the long-term safety study in patients age 12-17 years. Considering the favorable short term safety results, consistent between younger and older pediatric patients, I believe it is reasonable to extrapolate the long-term safety study from the adolescent population to the younger patients.

Recommended Regulatory Action

I recommend approval, extending the indication to pediatric patients age 6-17 years.

Risk Benefit Assessment

This sNDA provides substantial evidence of safety and effectiveness of Maxalt for the acute treatment of migraine in pediatric patients age 6-17 years. No new safety finding of concern was identified in the pediatric population.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

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