MEMORANDUM

DATE: December 12, 2011

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 20-865/S-020 & NDA 20-864/S-018

SUBJECT: Action Memo for NDA 20-865/S-020 & NDA 20-864/S-018, for the use of Maxalt-MLT (rizatriptan) orally disintegrating tablet and Maxalt (rizatriptan) tablet, respectively, in the acute treatment of migraine in pediatric patients ages 6-17 years old

NDA 20-865/S-020 & NDA 20-864/S-018, for the use of Maxalt-MLT (rizatriptan) orally disintegrating tablet and Maxalt (rizatriptan) tablet, respectively, in the acute treatment of migraine in pediatric patients, were submitted by Merck Sharp & Dohme Corp. on 3/25/2011. Both formulations are currently approved for the acute treatment of migraine in adults. The submissions contained reports of a randomized controlled trial in patients ages 12-17, and were submitted in response to a Pediatric Written Request (PWR). Ultimately, the applications were amended to include data from the controlled trial in patients down to the age of 6 years. The applications also contain safety data, as well as pharmacokinetic data in the pediatric population.

The applications have been reviewed by Dr. Nushin Todd, medical reviewer, Dr. Mary Doi, safety reviewer, Melissa Hulett, Division of Risk Management, Dr. Xiang Ling, statistical reviewer, Dr. Xinning Yang, clinical pharmacology reviewer, and Dr Eric Bastings, deputy division director, and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved.

Briefly, as described by Dr. Bastings, the sponsor had previously performed two randomized controlled trials in pediatric patients, but neither was positive. Presumably, the sponsor concluded that the primary reason that these studies failed was related to underdosing in heavier children. For this, and other reasons, the division decided to issue a PWR for an adequately designed study (including weight-based dosing and an enrichment maneuver; see below). The controlled study included patients from the ages of 6-17 years old, but the initial submission contained the results only from the portion of the study that included 12-17 years old. For reasons discussed by Dr. Bastings, the PWR required only the results of a study in this latter age group. With the 120 day safety update, however, the sponsor submitted the results for the 6-11 year old patients, as well as the results combined for the 6-17 year olds. Given that the study was ultimately designed to include all enrolled patients from 6-17 years old, the primary analyses were of this combined dataset, despite the fact that both Drs.

Ling and Bastings performed initial analyses of data in the initial submission (i.e., 12-17 year olds).

The trial was a multi-center study in which patients with a moderate or severe headache were first randomized to placebo or Maxalt ODT, 5 mg for patients <40 kg or 10 mg for patients greater than or equal to 40 kg (these doses were designed to produce plasma levels of drug [Cmax and AUC] about equal to a 10 mg dose in adults) in a 20:1 ratio. Patients who received active drug who did not achieve mild or no pain at 15 minutes were re-randomized to Maxalt or placebo. The percentage of patients who were pain free at 2 hours after the second randomization was the primary outcome, with the typical associated symptoms (percent nausea-, photophobia-, and phonophobia-free) considered secondary outcomes, as was the percent of patients who achieved either mild or no pain at 2 hours (the division has accepted a single primary outcome in pediatric patients, as opposed to the typical requirement in adults for significant findings on all four outcomes described above).

A total of 1382 patients were randomized in the first phase, and 819 (rizatriptan 409, placebo 410) were randomized in the second phase.

The following table presents the results for the primary outcome, percent of patients pain-free at 2 hours:

Age	Maxalt	Placebo	p-value
6-17	126/382 (33%)	94/388 (24%)	0.01
6-11	39/98 (40%)	31/102 (30%)	0.27
12-17	87/284 (31%)	63/286 (22%)	0.025

Although other endpoints typically trended in favor of Maxalt, they did not reach nominal statistical significance.

Although the percent of patients pain-free at 2 hours differed somewhat by weight category, they both favored rizatriptan over placebo:

Weight Category	Rizatriptan	Placebo
<40 kg	39.4% (39/99)	36.7% (33/90)
>40 kg	30.7% (87/283)	20.5% (61/298)

There were no safety issues identified that were unique to the pediatric population, or that would preclude approval.

Because the ODT and tablet formulations are bioequivalent, the results of this study apply to both formulations.

COMMENTS

The sponsor has submitted the results of a randomized trial in pediatric patients ages 6-17 years that has demonstrated a significant between-treatment difference on the primary outcome, percent of patients pain-free at 2 hours post-dosing. Other outcomes were consistent with this finding, though they did not reach statistical significance. The division has accepted these outcomes as establishing effectiveness in pediatric patients, given the previous data in adults.

For this reason, then, I will issue the attached Approval letter, with appended agreed-upon labeling. It should be noted that the labeling approved in this action contains language included in various labeling supplements submitted by the sponsor (NDA 20-865/S-016/S-018; NDA 20-864/S-016/S-017; see Dr. Doi's review of these supplements dated 9/8/11).

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
12/16/2011