DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 20-864

Merck Research Laboratories
Attention: David R. Hobbart, Ph.D
126 E. Lincoln Avenue
P.O. Box 2000, RY 33-206
Rahway, NJ 07065-0900

Dear Mr. Hobbart:

Reference is made to your October 27, 2007 Proposed Pediatric Study Request for Maxalt (rizatriptan benzoate).

To obtain needed pediatric information on rizatriptan benzoate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies:

1. Non clinical studies

To provide additional safety information for labeling, you must conduct a juvenile animal toxicity study in rat. This study must utilize animals of an age range and stage(s) of development that are comparable to the intended human population, and the animals must be exposed to the drug for a period that will cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate the effects of your drug on growth, reproductive development, and neurological and neurobehavioral development. Reproductive performance must be evaluated following cessation of treatment; there must be a washout period of appropriate duration (based on the half-life) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects must be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals must be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests must assess sensory function, motor function, and learning and memory. The neuropathological evaluation must include examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult.

We strongly encourage you to submit a protocol for the juvenile toxicity study to the Division for comment prior to initiation.

2. Clinical Studies

Type of studies
Study 1: Safety/Tolerability/Pharmacokinetic Study
Study 2: Pediatric Efficacy Study
Study 3: Pediatric Long-Term Safety Study

These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Objectives/rationale
Study 1: To assess the safety and tolerability of single doses of rizatriptan benzoate, and evaluate the pharmacokinetics of rizatriptan benzoate in pediatric migraineurs 6 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 6 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 6 to 17 years of age with a history of migraine headaches.

Indication(s) to be studied
The use of rizatriptan benzoate for the acute treatment of migraine in pediatric patients 6 to 17 years of age with a history of migraine headaches.

Study design
Study 1: Single dose, safety, tolerability and pharmacokinetic study in pediatric migraineurs 6 to 17 years of age, designed to compare the pharmacokinetic results in pediatric migraineurs with appropriate adult historical control data.
Study 2: Randomized, double-blind, placebo-controlled, parallel group outpatient study in pediatric migraineurs 6 to 17 years of age. The study design must take into account the short duration of migraine attacks, and the high placebo response rate in pediatric patients. The dose(s) evaluated and study design must be justified based on prior rizatriptan benzoate adult and pediatric efficacy and safety studies, published literature, and the results of Study 1. The protocol must allow the use of appropriate rescue medication after a suitable post-dosing interval.
Study 3: Open label, 12-month outpatient study in pediatric migraineurs 6 to 17 years of age.

Age groups to be studied
Pediatric patients 6 to 17 years of age, inclusive.

Number of patients to be studied or power of the study to be achieved
Study 1: At least 6 children with body weight<40 kg and 6 children with body weight≥40 kg must be evaluated. The ages must be distributed across the age range. There must be a similar number of male and female patients.
Study 2: The study must have 80% power to demonstrate an active treatment vs. placebo difference of eleven percentage points for the proportion of patients with pain freedom at 2 hours (with a two-sided type I error rate of 0.05). There must be similar number of patients in the <40 kg and ≥40 kg subgroups.

Study 3: At a minimum, 300 patients, using an effective dose, must be exposed for six months, and 100 patients, using an effective dose, must be exposed for one year. There must be a similar number of patients in the <40 kg and ≥40 kg subgroups. Patients must treat, on average, approximately 1 or more headache(s) per month for the six or twelve months period. At least half of the experience must be at the highest recommended dose.

Entry criteria
Study 1: Pediatric patients between 6 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the International Headache Society (IHS) current classification.
Study 2: Pediatric patients between 6 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the IHS current classification
Study 3: Pediatric patients between 6 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the IHS current classification.

Clinical endpoints
Study 1: Appropriately frequent standard measures of safety (including physical examinations, vital signs, and adverse reactions monitoring). Plasma concentrations of rizatriptan must be determined. Pharmacokinetic parameters including Cmax, tmax, AUC, t ½, Cl/F and Vd must be calculated and the mean clearance and apparent volume of distribution must be estimated within a standard error of 20% or less for both weight-based subgroups (<40 kg and ≥40 kg). Covariates such as age, body weight, body surface area, gender, and concomitant medications should be studied as appropriate. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under http://www.fda.gov/cder/guidance/1970dft.pdf.
Study 2: The primary efficacy endpoint must be pain freedom at 2 hours post-dose. Additional standard secondary migraine efficacy measures (including freedom from photophobia, phonophobia, or nausea, and use of rescue medication), and standard measures of safety must be included (e.g. physical examinations, vital signs, 12-lead ECG, adverse reactions monitoring, and laboratory safety tests including hematology, chemistry, urinalysis, and pregnancy test for females of childbearing potential). The study protocol must be submitted as part of a special protocol for Agency review and concurrence prior to initiating the study.
Study 3: Appropriately frequent standard measures of safety (including physical examinations, vital signs, 12-lead ECG, adverse reactions monitoring, and laboratory safety tests including hematology, chemistry, urinalysis, and pregnancy test for females of childbearing potential).

Study evaluations
Study 1: Safety data as discussed above. Reports of relevant pharmacokinetic parameters.
Study 2: Safety and effectiveness data through 24 hours post-dose.
Study 3: Safety data as discussed above.

Drug information:
Dosage form: Tablet.
Route of administration: oral
Regimen: To be determined by the development program
Formulation: ODT.

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if

it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Statistical information:
Study 1: Descriptive analysis of the safety data. Pharmacokinetic parameters including comparison to historic data from adults.
Study 2: Assessment of the between group difference on the primary endpoint by a pre-specified statistical methodology appropriate to the data generated. A subgroup analysis for patients <40 kg and ≥40 kg must be included. The protocol must include a plan for an interim analysis to reassess whether the study is adequately powered and must include a provision to adjust the sample size to have adequate power. Descriptive analysis of the safety data.
Study 3: Descriptive analysis of the safety data.

Labeling that may result from these studies:
You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that rizatriptan is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

***Format of reports to be submitted*:**

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before December 31, 2010. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:
Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Lana Chen, Regulatory Project Manager, at 301-796-1056.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple

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