



WRITTEN REQUEST – AMENDMENT 1

NDA 20-864

NDA 20-865

IND- (b) (4)

Merck Research Laboratories
Attention: Chitkala Kalidas, Ph.D.
Directory, Worldwide Regulatory Affairs
351, N. Sumneytown Pike
North Wales, PA 19454-2505

Dear Dr. Kalidas:

Please refer to your correspondence dated August 26, 2009, requesting changes to FDA's March 6, 2009 Written Request for pediatric studies for Maxalt® (rizatriptan benzoate).

The original Pediatric Written Request (dated 6-Mar-2009) required evaluation of patients 6-17 years of age. You provided an argument that the enrollment of patients 6-11 years of age poses significant operational challenges, making it not feasible to complete the pediatric program in the time frame allowed by BPCA. You cited numerous critical issues that influence the enrollment of patients in the age group of 6-11 years, including that the prevalence of migraine in this population is relatively low, pediatric migraineurs and their parents often do not seek medical attention for diagnosis and treatment of their migraines, and that parents may also be reluctant to enroll their young children into investigational studies. In the absence of adequate benchmarking data on the enrollment of younger patients, you assessed program feasibility through a questionnaire and interview of clinical sites, and determined that a sufficient number of qualified sites could not be identified in order to meet the enrollment requirements in the patient population aged 6-11 years and allow completion of the studies by March 31, 2011. The Agency has reviewed your argument, and agrees with your conclusions. Therefore, we are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 6, 2009, remain the same. (Text added is underlined. Text deleted is strikethrough.)

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

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 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 6 to 17 years of age with a history of migraine headaches.~~

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 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 12 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.~~

The use of rizatriptan benzoate for the acute treatment of migraine in pediatric patients 12 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 1: Single dose, safety, tolerability and pharmacokinetic study in pediatric migraineurs 12 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 2: Randomized, double-blind, placebo-controlled, parallel group outpatient study in pediatric migraineurs 12 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.~~

Study 3: Open label, 6-month outpatient study in pediatric migraineurs 12 to 17 years of age. This 6-month study is part of an open label 12-month outpatient study. This Written Request, however, is only requiring submission of 6-month, interim report of data by the filing date.

Age groups to be studied

Pediatric patients 6 to 17 years of age, inclusive.

Pediatric patients 12 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 \geq 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 1: At least 12 children 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 \geq 40 kg subgroups.~~

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). Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age.

~~**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 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 month period. At least half of the experience must be at the highest recommended dose.~~

Study 3: At a minimum, 300 patients, using an effective dose, must be exposed for six months. Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age. Patients must treat, on average, approximately 1 or more headache(s) per month for the six 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 1: Pediatric patients between 12 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 2: Pediatric patients between 12 and 17 years of age; diagnosis of migraine with or without aura, as defined by the IHS current classification; history of migraine attacks for more than 6 months; ≥ 1 to ≤ 8 moderate to severe migraine attacks per month in the 2 months prior to screening; duration of a typical untreated migraine attack (excluding sleep) of ≥3 hours.

~~**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.~~

Study 3: Pediatric patients between 12 and 17 years of age; diagnosis of migraine with or without aura, as defined by the IHS current classification; history of migraine attacks for more than 6 months; ≥ 1 to ≤ 8 moderate to severe migraine attacks per month in the 2 months prior to screening.

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 C_{max}, t_{max}, AUC, t_{1/2}, Cl/F and V_d 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/cedr/guidance/1970dft.pdf>.~~

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 C_{max}, t_{max}, AUC, t_{1/2}, Cl/F and V_d must be calculated and the mean clearance and apparent volume of distribution must be estimated within a standard error of 20% or less. Covariates such as age, body weight, body surface area, gender, and concomitant medications must be

studied. 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 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).

Statistical information:

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.

Study 2: Assessment of the between group difference on the primary endpoint by a pre-specified statistical methodology appropriate to the data generated. 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.

~~**Study 3:** Descriptive analysis of the safety data.~~

Study 3: Descriptive analysis of the safety data will be provided.

Timeframe for submitting reports of the studies:

~~Reports of the above studies must be submitted to the Agency on or before December 31, 2009. 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.~~

Reports of the above studies must be submitted to the Agency on or before March 31, 2011. 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.

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For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 6, 2009, as amended by this letter must be submitted to the Agency on or before March 31, 2011, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) [please verify number] or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

Attachment (Complete Copy of Written Request as amended)

WRITTEN REQUEST

NDA 20-864
NDA 20-865

Merck Research Laboratories
Attention: Chitkala Kalidas, Ph.D.
Directory, Worldwide Regulatory Affairs
351, N. Sumneytown Pike
North Wales, PA 19454-2505

Dear Dr. Kalidas:

Please refer to your correspondence dated August 26, 2009, requesting changes to FDA's March 6, 2009 Written Request for pediatric studies for Maxalt® (rizatriptan benzoate).

Written Request for Maxalt® (rizatriptan benzoate)

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 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.

Indication(s) to be studied

The use of rizatriptan benzoate for the acute treatment of migraine in pediatric patients 12 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 12 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 12 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, 6-month outpatient study in pediatric migraineurs 12 to 17 years of age. This 6-month study is part of an open label 12-month outpatient study. This Written Request, however, is only requiring submission of 6-month, interim report of data by the filing date.

Age groups to be studied

Pediatric patients 12 to 17 years of age, inclusive.

Number of patients to be studied or power of the study to be achieved

Study 1: At least 12 children 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). Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age.

Study 3: At a minimum, 300 patients, using an effective dose, must be exposed for six months. Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age. Patients must treat, on average, approximately 1 or more headache(s) per month for the six months period. At least half of the experience must be at the highest recommended dose.

Entry criteria

Study 1: Pediatric patients between 12 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 12 and 17 years of age; diagnosis of migraine with or without aura, as defined by the IHS current classification; history of migraine attacks for more than 6 months; ≥ 1 to ≤ 8 moderate to severe migraine attacks per month in the 2 months prior to screening; duration of a typical untreated migraine attack (excluding sleep) of ≥ 3 hours.

Study 3: Pediatric patients between 12 and 17 years of age; diagnosis of migraine with or without aura, as defined by the IHS current classification; history of migraine attacks for more than 6 months; ≥ 1 to ≤ 8 moderate to severe migraine attacks per month in the 2 months prior to screening.

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 C_{max}, t_{max}, AUC, t_{1/2}, Cl/F and V_d must be calculated and the mean clearance and apparent volume of distribution must be estimated within a standard error of 20% or less. Covariates such as age, body weight, body surface area, gender, and concomitant medications must be studied. 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).

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. 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.

Study 3: Descriptive analysis of the safety data will be provided.

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 March 31, 2011. 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>

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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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20864	GI-1	MERCK AND CO INC	MAXALT(RIZATRIPTAN BENZOATE)5MG/10MG TAB
NDA-20865	GI-1	MERCK AND CO INC	MAXALT (RIZATRIPTAN BENZOATE) RAPIDISC

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

/s/

LANA Y CHEN
01/13/2010

ROBERT TEMPLE
01/13/2010