DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-926

WRITTEN REQUEST

GlaxoSmithKline
Attention: Elizabeth A. McConnell, Pharm.D.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Reference is made to your July 19, 2013, Proposed Pediatric Study Request for sumatriptan and naproxen. Reference is also made to the Written Request the Food and Drug Administration (FDA) issued on June 27, 2007, which expired December 1, 2010, subsequent meetings between FDA and GlaxoSmithKline related to that Written Request, and Study 1, Study 2, and Study 3, which were completed at that time to partially fulfill the terms of the Written Request. (b) (4) Therefore, Study 1, Study 2, and Study 3 are those which we are requesting under this new Written Request.

To obtain needed pediatric information on sumatriptan and naproxen, FDA is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of studies
Study 1: Adolescent Pharmacokinetic Study
Study 2: Adolescent Efficacy Study
Study 3: Adolescent Long-Term Safety Study

Objectives/rationale
Study 1: To evaluate the pharmacokinetics of sumatriptan and naproxen in adolescents 12 to 17 years of age with a history of migraine and to evaluate the pharmacokinetics compared to adults (historical controls).
Study 2: To evaluate the efficacy and safety of sumatriptan and naproxen in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.
Study 3: To evaluate the long-term safety of sumatriptan and naproxen in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.

Indication to be studied
The use of sumatriptan and naproxen tablets for the acute treatment of migraine in adolescents 12 to 17 years of age with a history of migraine headaches.

Study design
Study 1: Single dose, inpatient, pharmacokinetic study in adolescents with a history of migraine, which compares the results with appropriate adult historical control data.
Study 2: Randomized, double-blind, placebo-controlled, parallel group outpatient study in adolescents with a history of migraine headaches. The study must attempt to define the dose-response relationship in this age group, including the identification of a no-effect dose. 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 adolescents with a history of migraine headaches.

Age groups to be studied
Adolescent patients ages 12 to 17 years, inclusive.

Number of patients to be studied or power of the study to be achieved
Study 1: A sufficient number of adolescent migraine patients to adequately characterize the single dose pharmacokinetics of adolescents compared to adults. The ages should be uniformly distributed across the age range. There must be a reasonable distribution of both sexes in this age bracket. If a traditional pharmacokinetic study is conducted (frequent sampling), the number of subjects would be approximately 6-12 for each dose evaluated.
Study 2: A sufficient number of adolescent migraine patients to be able to detect a clinically significant difference between treatment and control on a valid measure of efficacy. There must be similar number of patients in the 12 to 14 and 15 to 17 age groups. The study must be powered to detect an effect size similar to that seen in the adult population.
Study 3: A sufficient number of adolescent migraine patients to be able to characterize the long-term safety of Treximet (sumatriptan and naproxen) when used to treat multiple migraine attacks over one year. Each patient must treat, on average, approximately 1 or more headaches per month for six to twelve months. At a minimum, 200 patients, using an effective dose, must be exposed for six months, and 75 patients, using an effective dose, must be exposed for one year. There must be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease 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.

Entry criteria
Study 1: Adolescent 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: Adolescent patients between 12 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the IHS current classification.
Study 3: Adolescent patients between 12 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: Plasma concentrations of sumatriptan and naproxen must be determined. Pharmacokinetic parameters including Cmax, tmax, AUC, t ½, and Cl/F must be calculated and covariates such as age, body weight, body surface area, gender, and concomitant medications must be studied as appropriate. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at http://www.fda.gov/cder/guidance/1970dft.pdf.
Study 2: The primary endpoint must be a reasonable measure of acute migraine relief in this population, and must be submitted as part of a special protocol for Agency review and concurrence prior to initiating the study. Additional standard secondary migraine efficacy measures and standard measures of safety (clinical – including signs and symptoms, and laboratory) must be included.
Study 3: Appropriately frequent standard measures of safety (clinical – including signs and symptoms, and laboratory).

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

Extraordinary results: In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug information:
Dosage form: Tablet. If different formulations are used in the clinical trials compared to the to-be-marketed formulation, the relative bioavailability between the formulations must be assessed (the use of bioavailability data generated in adults is acceptable).
Route of administration: oral
Regimen: To be determined by the development program
Formulation: Use an age-appropriate formulation in the studies 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.

In accordance with section 505A(e)(2), 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 approval);
2) the Agency grants pediatric exclusivity, including publishing 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 indicating you have not marketed the new pediatric formulation.

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 pharmacokinetic parameters and comparison to historic data from adults.
Study 2: Assessment of the between group difference on the primary endpoint by a statistical methodology appropriate to the data generated.
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 studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate sumatriptan and naproxen 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 studies. 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 studies.

Format of reports to be submitted:
You must submit full study reports (which in the current situation consist of the full study reports that, as discussed above, previously were submitted as General Correspondence and subsequently withdrawn pursuant to discussions with FDA) 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. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event

report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 November 30, 2014. 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 studies, 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 studies 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 studies must 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, complete response); 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/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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}

Ellis Unger, 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/

ELLIS F UNGER
08/18/2014