Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 22037

Shire Development, Inc.
Attention: James Ewing
Manager, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Mr. Ewing:

Reference is made to your May 3, 2007 Proposed Pediatric Study Request for guanfacine hydrochloride

Background

This study will investigate the potential use of Intuniv® (guanfacine hydrochloride extended-release) monotherapy in the treatment of adolescents (ages 13 to 17 years) with a diagnosis of Attention Deficit-Hyperactivity Disorder (ADHD).

In the original NDA, studies demonstrated the efficacy of guanfacine monotherapy, overall, in a study population consisting of children and adolescents between the ages of 6 and 17 years. A subgroup analysis demonstrated efficacy in the subpopulation of children (ages 6 to 12 years). However, the subgroup analysis did not confirm the efficacy of guanfacine in the subpopulation of adolescents (ages 13 to 17 years). This differential effect may have been related to the fixed-dose, non-weight-based dosing strategy and the weight-dependent pharmacokinetics of guanfacine. In essence, a number of adolescent subjects may have been underdosed, because of randomization to low, fixed doses. Although this is a likely explanation of the efficacy findings, it would be useful to have data from an adequate and well controlled trial to confirm that guanfacine is efficacious in the treatment of adolescents with ADHD.

We acknowledge that you have submitted adequate safety data from long-term safety studies with guanfacine monotherapy. We also acknowledge that you have submitted adequate pharmacokinetic data from monotherapy studies in children and adolescents. In addition, we acknowledge that you have submitted data from two pharmacokinetic drug-drug interaction studies of guanfacine and stimulant co-administration in adult patients (one using a methylphenidate product and one using an amphetamine product).

To obtain needed pediatric information on guanfacine monotherapy in the treatment of adolescents with Attention Deficit-Hyperactivity Disorder, 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 described below.

Specific Study Requirements for Development Program

Overall Objectives/Rationale

The overall goal of the development program should be to obtain adequate and well controlled data regarding the safety and efficacy of guanfacine monotherapy in adolescents (ages 13 to 17 years) with a diagnosis of Attention Deficit-Hyperactivity Disorder.

Study Design

Pediatric Efficacy and Safety Study

For the controlled efficacy and safety study requirement, you must conduct one randomized, double-blind, placebo-controlled, parallel-group, trial in adolescents (13 to 17 years) with ADHD. The primary goals of the study will be: 1) to evaluate the efficacy of guanfacine on the symptoms of ADHD in this population; 2) to evaluate whether there are dose-response relationships for efficacy and safety; and 3) to evaluate the safety and tolerability of guanfacine in this population. You are required to employ a weight-based dosing strategy in the trial, because there is a strong inverse correlation between body weight and guanfacine serum exposures in children and adolescents. The study should allow a characterization of potential dose-response or exposure-response relationships to inform labeling recommendations on dosing. We recommend a fixed-dose study with doses selected based on body weight.

You must perform pharmacometrics-based modeling and simulation to inform the study design. Specifically, you must conduct a dose (or exposure)-response analysis for adolescent patients, taking into account the time course of ADHD-RS-IV scores for the placebo and active treatment groups. The model then must be employed to simulate the ADHD-RS-IV scores under the proposed design. You must obtain agreement from the FDA on the resultant study design prior to initiating the study.

At least 50% of subjects assigned to active drug must complete to the nominal endpoint of the trial in order for the trials to be considered completed and, therefore, responsive to this request. Information about the reasons for subjects discontinuing from the trial must be collected and provided. The trial must maximize the opportunity to detect a treatment effect of the drug in this population.

Patients to be Studied

Age group in which study will be performed

You must include adolescents (ages 13 to 17 years) with a diagnosis of ADHD. The gender distribution of participants in this study must reflect the distribution in those affected with ADHD.

Number of patients to be studied

Pediatric Efficacy and Safety Study

Your study must be designed with at least 85% statistical power to be able to detect a clinically meaningful treatment benefit on the primary endpoint at a conventional level (alpha=0.05, 2-tailed) of statistical significance. If you intend to use the change from baseline in the ADHD-RS-IV total score as the primary efficacy endpoint, a 4-point difference between guanfacine and placebo will be considered a clinically meaningful treatment effect size.

Representation of Ethnic and Racial Minorities

The studies must take into account adequate (e.g., proportionate to disease population) representation of adolescents 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

The protocol must include a valid and reliable diagnostic method for recruiting and enrolling children and adolescents meeting DSM-IV criteria for ADHD.

Patient Evaluations and Study Endpoints

Pediatric Efficacy and Safety Study

Efficacy Endpoints

We recommend that you use a validated instrument specific to ADHD and sensitive to drug effects in the target population. The ADHD Rating Scale-IV (ADHD-RS-IV) would be acceptable. You must prospectively identify a primary outcome for the controlled efficacy trial; ordinarily, this would be the change from baseline to endpoint on the specific symptom rating scale you have chosen for your trial.

Safety Endpoints

Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., adverse events monitoring, sitting and standing vital signs (pulse rate and blood pressure), weight, height (as measured by stadiometer), clinical laboratory measures (chemistry, liver function tests, hematology, and urinalysis), and ECGs. You must provide an assessment of psychiatric adverse events (i.e. worsening of ADHD symptoms, hallucinations, depressed mood, and suicidality). For the assessment of psychiatric and behavioral adverse events, you must propose assessment instruments to incorporate in the study. You must systematically and prospectively assess for suicidality using a validated instrument, such as the Columbia Suicide Severity Rating Scale (C-SSRS). You must collect adverse events data regarding the following safety

concerns with guanfacine: orthostatic hypotension, hypotension, bradycardia, syncope, sedation/somnolence, and weight gain.

PK Endpoints
Informative sparse PK samples must be collected in and an exposure-response analysis for both effectiveness and key safety variables must be conducted. You must obtain agreement from the FDA on the PK sampling scheme.

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.

Statistical information, including power of study and statistical assessments

Pediatric Efficacy and Safety Studies:

- The study must have a detailed statistical plan; this plan must be submitted for comment prior to initiation of the study, or early in the conduct of the study. The study must be designed with at least 85% statistical power to be able to detect a clinically meaningful treatment benefit on the primary end point at a conventional level (alpha=0.05, 2- tailed) of statistical significance. If you intend to use the change from baseline in the ADHD-RS-IV total score as the primary efficacy endpoint, a 4-point difference between guanfacine and placebo will be considered a clinically meaningful treatment effect size. You must obtain agreement on the final statistical plan prior to 25% enrollment, including the pre-specified rule to obtain the variance estimate and to adjust the sample size.

- To fulfill the pediatric written request, you must have an interim analysis for sample size re-estimation to ensure sufficient study power. You must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed when the study is close to finishing (for example, at > 80% of initially planned enrollment). Options for estimating variability are (1) a blinded, pooled analysis of all groups, or (2) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for this interim analysis to assess the variability, but if you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment is required.

Labeling that may result from the studies

You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrates that guanfacine is safe and effective, or whether such study results are inconclusive in the studied pediatric population or subpopulation, the labeling must include information about the results of the study. 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.

Format and types 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 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 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 study

Reports of the above studies must be submitted to the Agency within 5 years of the date of this letter. 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. 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, 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 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 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, 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 Shin-Ye Sandy Chang, Regulatory Project Manager, at 301-796-3971.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation 1
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
04/01/2011