DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22037 **NDA APPROVAL**

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

Dear Mr. Ewing:

Please refer to your new drug application (NDA) dated and received August 24, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Intuniv (guanfacine) extended-release 1 mg, 2 mg, 3 mg, and 4 mg tablets.

We acknowledge receipt of your submissions dated June 27, 2007, July 23, 31, 2007, August 20, 2007, September 18, 2007, October 1, 2007, February 15, 2008, January 26, 2009, February 5, 2009, April 15, 22, 24, 2009, May 13, 2009, June 4, 2009, and July 13, 14, 22, 28 , 2009.

The July 28, 2009 submission constituted a complete response to our July 27, 2009 action letter.

This new drug application provides for the use of Intuniv (guanfacine) extended-release tablets for Attention Deficit Hyperactivity Disorder (ADHD) in children between 6 years to 17 years of age.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm155657.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-037**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as agreed upon in your communication dated August 26, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-037**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Intuniv, for this product

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 5 years of age because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

- The diagnostic criteria and assessment measures for determining efficacy for the treatment of ADHD in children less than 6 years old are not well defined.
- Pharmaceutical treatment in this age group is uncommon.
- Intuniv is a solid dose, matrix, extended-release formulation, available in 1 mg, 2 mg, 3 mg, and 4 mg strengths, and its tablets cannot be subdivided. Since a liquid/rapid-melt form and additional strengths are not available, it is not expected that the product will be prescribed for potential ADHD patients less than 6 years old.

We are deferring submission of the additional pediatric studies for ages 6 to 17, and 12-17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

- ADHD is a chronic condition and is almost a certainty that patients who respond in short-term treatment will be extended for much longer treatment
- Current studies failed to demonstrate efficacy in adolescents, most likely due to less than optimal exposures. An additional trial in adolescents with ADHD is to confirm efficacy in this population group.

- It is likely that this product will be used as an adjunct to stimulant therapy in patients who have only responded partially to this class of drugs.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1538-1 Deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17. A long-term maintenance study of efficacy and safety of guanfacine as monotherapy in children and adolescents

Final Report Submission: September 2012

1538-2 Deferred pediatric study under PREA for the treatment of Attention Deficit ` Hyperactivity Disorder (ADHD) in adolescent patients ages 12 to 17. An efficacy and safety study of guanfacine in adolescents.

Final Report Submission: September 2012

1538-3 Deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17. An efficacy and safety study of guanfacine as adjunctive treatment with long-acting oral psychostimulants.

Final Report Submission: June 2010

Submit all final reports to this NDA. Use the following designator to prominently label all submissions**: "Required Pediatric Assessment(s)"**.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected signal of cardiac valvulopathy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this(ese) serious risk(s).

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

Pharmacology/Toxicology

1538-4 Conduct a cardiac toxicity study in rats

In view of a recent publication reporting that guanfacine acts as an agonist at the serotonin 5 HT2B receptor (Huang, X-P, et al., Molecular Pharmacology Fast Forward, July 1, 2009), in combination with the purported link between cardiac valvulopathy and 5-HT2B agonists, you are required to conduct a study in rats to test whether guanfacine produces valvulopathy. This study will include doses of guanfacine up to a maximum tolerated dose (MTD), positive and negative controls, and assessment of systemic drug exposures. If valvulopathy is observed, establish a NOEL(s).

Final Protocol Submission:	March 2010
Study Initiation:	September 2010
Final Report Submission:	September 2011

1538-5 Conduct reproductive toxicity assessment in juvenile rats

In order to address the inadequacy of the assessment of guanfacine's effects on the reproductive system in your original (monotherapy) juvenile rat study, assess the effects of guanfacine on mating and fertility in the guanfacine monotherapy arm of your proposed juvenile rat study of guanfacine in combination with stimulant(s). We acknowledge your communication (7/20/09) indicating that this study has been completed, including the histopathology.

Final Report Submission:	March 2010

Submit all final report(s) to this NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission**,** as appropriate:

- **REQUIRED POSTMARKETING INTERIM REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii) . We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF Section 506B

We remind you of your postmarketing commitment in your submission dated July 28, 2009. This commitment is listed below.

Chemistry, Manufacturing, and Controls

1538-6 Within one year of the product approval, you will re-evaluate the dissolution specification (in particular, the last sample point), based on all batches manufactured during the time period. An updated dissolution specification should be submitted if the data justifies a change in the current proposed specification

Final Report Submission: September 2010

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence.**"

DISSOLUTION METHOD AND SPECIFICATION

We remind you of the proposed dissolution method submitted to the Agency on January 26, 2009, and accepted June 30, 2009.

Method

Apparatus:	USP Apparatus II
Speed:	75 rpm
Medium:	pH 2.2 HCL buffer

Specification

Time	Criteria
1 hour	*(b) (4)*

4 hours	(b) (4)
8 hours	(b) (4)
24 hours	not less than (b) (4)

EXPIRY DATE

An expiration of 48 months has been granted.

SPECIAL REPORTING REQUIREMENTS FOR SELECTED SPONTANEOUS REPORTS

In order to facilitate our efficient review and evaluation of data pertinent to valvulopathy, we ask that you submit any spontaneous reports for adverse events of this type as 15 day reports.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

THOMAS P LAUGHREN
09/02/2009