CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-037

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22037

COMPLETE RESPONSE

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 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 January 26, 2009, April 15, 22, 24, 2009, May 8, 13, 2009, June 4, 2009, and July 13, 2009.

The January 26, 2009 amendment constituted a complete response to our June 20, 2007 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 the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm155657.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

CARTON AND CONTAINER LABELS

Please submit draft carton and container labeling revised as follows:

- The base container label must include the proprietary name, established name, dosage form, and strength statement. Otherwise, when the peel back label is removed, there is no identifying product information on the base label securely affixed directly to the sample containers.
- Include the statement 'XX mg per tablet' or 'Each tablet contains XX mg' on the principal display panel of the 'peel back' and 'base' container labels. This will better inform patients that 1 mg or 2 mg is contained in each tablet. As presented, a patient or caregiver may incorrectly interpret the product strength represents the total content in all 7 tablets (e.g. 1 mg = 7 tablets). Although the statement, 'Each tablet contains XX mg of guanfacine as guanfacine HCl' is included on the inside of the peel back label, patients and/or caregivers may fail to peel back the top label to read this important dosing information.
- Use a darker font color to improve the readability and presentation of the established name. As currently presented, the red font color against the white background gives the name a blurred appearance and makes it difficult to read

DISSOLUTION METHOD AND SPECIFICATION

We remind you of the proposed dissolution method submitted to the Agency on January 26, 2009, and accepted June 9, 2009.

Method

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

Specification

Time	Criteria
1 hour	(b) (4)
4 hours	
8 hours	
(b) (4)	not less than (b) (6)

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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: Labeling

22 pp withheld in full immediately after this page as (b)(4) Draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-037

Shire Development Inc.
Attention: Michael S. Spitz, RAC
Senior Management, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Mr. Spitz:

Please refer to your August 24, 2006 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, (b) (4), 3 mg, (b) (4) and 4 mg Extended-Release Tablets.

We acknowledge receipt of your submissions dated October 4, 2006, November 7, 10, 21, 2006, December 20, 21, 2006, January 23, 2007, February 9, 13, 23, 2007, March 6, 12, 16, 20, 2007, April 120, 23, 2007, May 24, 25, 29, 2007 and June 5, 2007.

This new drug application provides for the use of Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, (b) (4) mg, 3 mg, (b) mg and 4 mg Extended-Release Tablets for the treatment of attention deficit hyperactivity disorder (ADHD).

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies and respond to our requests listed below:

Office of Clinical Pharmacology:

- (b) (4)
- (b) (4)
- Please provide a justification for the choice of dissolution media. The use of a high concentration of (b) (4) is not justified because guanfacine is soluble at the proposed pH 2.2. Moreover, the use of (b) (4) makes the dissolution test less discriminating.

- Please perform dissolution specifications on an interim the basis until a new dissolution method without using a (b) (4) is proposed.

- (b) (4)

- In future clinical trials, we recommend that you collect blood samples for measuring guanfacine concentrations. Due to the wide range of body-weights of patients in the clinical trials, guanfacine concentrations would be more informative to understand issues related to clinical benefit (ADHD-RS-IV scores) and safety (lowering of blood pressure, heart rate and prolongation of QTc) than actual dose.

Dissolution Method and Specification

We ask that you agree to the following final dissolution method and specification for all strengths:

Apparatus:	USP Apparatus II (paddles)
Paddle Speed:	75rpm
Medium:	HCL buffer with 1% hexadecyltrimethylammonium bromide, pH 2.2
Temperature:	37.0°C
Dissolution Volume:	900mL

Specification:

Time (hr)	High Specification	Low Specification
1.0	(b) (4)	
4.0		
.0		
(b) (4)		

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Proprietary Name and Container Label

The Division of Medication Errors and Technical Support (DMETS) finds the proprietary name "Intuniv", acceptable. However, our approval of the proprietary name is tentative based upon the final date of NDA approval. If final approval of this application extends beyond September 2007, the name will be reevaluated by DMETS.

Additionally, we note that you have already addressed some of DMETS safety concerns regarding the labels and labeling. However, we continue to have the following areas in which we believe improvement is needed in order to minimize error.

A. GENERAL COMMENT

1. The color font used for the active ingredient "guanfacine" is less prominent than the dosage form, "extended release". Use a more prominent color for the active ingredient "guanfacine
HCl".

(b) (4)

2. Relocate the net quantity statement away from the established name and product strength, preferably toward the bottom of the principal display panel. This should aid in decreasing the risk of confusion between the net quantity and the product strengths.

3. The warning statement, *"Tablets should not be crushed, chewed or broken before swallowing",* is included in the package insert and patient counseling information labeling because this may increase the rate of release of the active drug. DMETS recommends that this important warning statement be included on the container label and carton labeling of Intuniv.

4. Insert a space between the numbers and unit of measure in each citation of product strength.
   For example, change (b) mg' to (b) mg".

B. Container Label

1. Each product strength is embedded in a geometric shape with a different background color. For example, the (b) mg, 3 mg, and 4 mg strengths are presented inside of circles or elongated semi-circles in different shades of green (see figure page 13). There is a concern that the strengths highlighted using similar colors and shapes, could easily be confused, leading to product selection errors and resulting in the dispensing or administration of the wrong strength. Additionally, DMETS does not believe that the background colors used for the different strengths are very distinguishable and may not aid in proper selection of the strength. DMETS recommends that each product strength have a different, distinguishable background color, to help practitioners more easily differentiate between the strengths of Intuniv, and thus reduce the potential for selection errors.

(b) (4)

2. We recommend increasing the prominence of the decimal point for the (b) mg and (b) mg product strengths. DMETS notes that the decimal point within the (b) mg and (b) mg strengths is difficult to see and may therefore cause the strengths to misinterpreted as (b) mg and (b) mg respectively.

(b) (4)

3. We recommend revising the colors of the container label for the 2 mg strength to provide greater color contrast, the white background for the yellow/gold font is difficult to read.

(b) (4)

Principal Display Panel of 2 mg Container Label

4. We recommend relocating the strength to appear in conjunction with the established name.

D. Insert Labeling

1. Highlights of Prescribing Information

a. Increase the prominence of the warning statement "*Tablets should not be crushed, chewed, or broken before swallowing*", in section 2.1 of Dosage and Administration, using a different font, font size, or uppercase letters, to emphasize the importance of this information.

b. Include units of measure (i.e. mg) following each notation of every strength listed in section (3) of Dosage Forms and Strengths. The strengths listed as 1, 2, (b) 3,

(b) and 4 mg should be revised to read 1 mg, 2 mg, (b) mg, 3 mg, (b) mg, and 4 mg.

2. Full Prescribing Information

   a. Increase the prominence of the warning statement "Tablets should not be crushed, chewed or broken before swallowing..." written in sections 2.1 General Dosing Information, 17.1 Dosing and Administration, and 17.3 FDA-approved patient labeling, using a different font, font size, or uppercase letters, to emphasize the importance of this instruction.

   b. Include units of measure (i.e. mg) following each notation of every strength listed in section 2.2 "Titration and Maintenance"; section 3 "Dosage Forms & Strengths"; section 6.1 "Clinical Trial Experience" (Short Term Clinical Studies and Long Term Clinical Studies sections); and section 16 "How Supplied/Storage & Handling", in accordance with recommendation D1b above.

   c. Delete the use of trailing zeros in the pharmacokinetic data found in section 12.3 "Pharmacokinetics on page 16. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. Trailing zeros are considered a dangerous abbreviation and are on the dangerous abbreviations list. Thus, we discourage the use of trailing zeros in labels and labeling, as the potential for a ten-fold dosing error exists if the decimal point is point is not readily apparent. Additionally, the use of terminal zeros in the expression of a strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO).

Risk Management Plan (RMP)

We request that you summarize in a section of the Periodic report or Periodic Safety Update Report (PSUR) all cases of abuse, misuse, and diversion regardless of whether an adverse event occurred. Sources of such cases include, but are not limited to, the toll-free line, the Internet Monitoring Program, News/Media monitoring, and the general information phone lines and direct emails. In addition, you should provide a summary in the Periodic report or PSUR of all other surveillance monitoring data (e.g., from Federal Surveys, School/Community Monitoring, DAWN Live! etc.). We also request that you send a desk copy of the report, via the usual method of sending desk copies, clearly identified for "OSE Risk Management Program Coordinator."

In addition, we ask that you commit to a RMP to explore for various safety problems observed in your development program, i.e., sedation, cognitive impairment, hypotension, syncope, bradycardia,, and QT prolongation. We would be happy to discuss such a program with you.

Postmarketing Commitments

- ADHD is a chronic condition and it is almost a certainty that patients who respond in short-term treatment will be extended for much longer-term treatment. Therefore, we ask that you commit to conducting a longer-term efficacy study with your product to explore the question of longer-term efficacy. A randomized withdrawal design would likely be the best approach.

- We have not limited the use of your product to children, despite the failure of your studies to demonstrate efficacy in adolescents, because we tend to agree that less than optimal exposures may have contributed to this outcome. Nevertheless, we ask that you commit to conducting an additional trial in adolescents with ADHD to confirm prospectively that your product is effective in this important population group.

- We also believe it is likely that your product will be used in adults with ADHD. In anticipation of such use, we ask that you commit to conducting an efficacy study of your product in adult ADHD.

- Given the likelihood that your product will be used as an adjunct to stimulant therapy in patients who have responded only partially to this class of drugs, we also ask that you commit to conducting a placebo-controlled adjunctive therapy study in ADHD.

- Due to the nature of the data on QT prolongation collected in your program thus far (no time matched placebo, inadequate baseline measurements, unknown food effects), we feel that the QT signal has not been adequately quantified. Thus, we ask that you commit to conducting a thorough QT study for a more definitive understanding of this effect.

- The published literature suggests that co-administration of guanfacine may result in higher concentrations of valproic acid. Since it is very likely that INTUNIV will be coadministered with valproic acid derivatives, we ask that you commit to conducting a study of the interaction of these drugs.

We would be happy to discuss any study proposals with you.

Foreign Regulatory Update

We require a review of the status of all Intuniv (guanfacine hydrochloride) actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Intuniv (guanfacine hydrochloride) has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Intuniv (guanfacine hydrochloride) along with English translations when needed.

Request for Safety and World Literature Update

Our assessment of the safety of Intuniv (guanfacine hydrochloride) is based on our review of all safety information provided in your original and subsequent submissions, including your safety update dated November 17, 2006. When you respond to the above deficiencies, include a safety update as described

at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide English translations of current approved foreign labeling not previously submitted.

7. Prior to the approval of Intuniv (guanfacine hydrochloride), we require an updated report on the world archival literature pertaining to the safety of Intuniv (guanfacine hydrochloride). We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Intuniv (guanfacine hydrochloride). The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Promotional Material

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly 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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved and scheduling is complete.

If you have any questions, call LT Felecia Curtis, R.N., Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

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

Attachment (Labeling)

29 pp withheld immediately following this page as (b)(4) draft labeling.

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

/s/

Thomas Laughren
6/20/2007 09:33:10 AM

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