M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 27, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for complete response action for SPD503 (guanfacine) extended release tablets for the treatment of attention deficit hyperactivity disorder (ADHD)

TO: File NDA 22-037
[Note: This overview should be filed with the 1-26-09 re-submission of this NDA.]

1.0 BACKGROUND

SPD503 is an extended release formulation of guanfacine, a selective alpha-2A-adrenergic receptor agonist. Guanfacine has been marketed in an immediate release form (Tenex) for the treatment of hypertension since 1986 (NDA 19-032). The proposed indication for SPD503 is for the treatment of ADHD. SPD503 is not a stimulant. Although the mechanism of action of this compound in ADHD is unknown, there is some evidence that selective alpha-2A-adrenergic receptor agonists act directly in the prefrontal cortex to enhance executive function. There has been fairly extensive off-label use of immediate release guanfacine for ADHD and also of clonidine, another alpha-2-adrenergic receptor agonist. The goal of this program was to develop a sustained release formulation of guanfacine to improve the tolerability and compliance with the use of this product, and to provide definitive evidence for its safety and efficacy. It is noteworthy that the only other available nonstimulant product for ADHD is atomoxetine, a selective NE reuptake inhibitor.

The sponsor's proposed dose range is 1 to 4 mg/day. The sponsor proposes that efficacy is observed in a plasma level range of 0.05 to 0.08 mg/kg/day, and that additional benefit may be seen in exposures up to 0.12 mg/kg/day. The available strengths would be: 1, 2, 3, and 4 mg.

We issued an approvable letter for this application on 6-10-07. That letter noted several deficiencies, including biopharmaceutic and carton labeling, and we requested that the sponsor address several other issues as well, including a RMP, a foreign regulatory update, and a safety update. We also asked the sponsor to address a number of issues as phase 4 commitments, including a maintenance study, an adolescent study, an adult ADHD study (we have subsequently agreed that this study is not needed), a study of guanfacine as adjunctive treatment

for ADHD (this study is ongoing), a thorough QT study (sponsor has conducted this study), and a DDI study with valproate (we have subsequently agreed that this study is not needed).

The sponsor resubmitted the application on 1-26-09.

2.0 CHEMISTRY

All of the CMC issues have been addressed, including the final site inspection, and the CMC group has recommended an approval action.

The acceptability of the proposed name "Intuniv" has been reafirmed by DMEPA.

3.0 PHARMACOLOGY

All of the pharm/tox issues have been addressed, and the pharm/tox group has recommended an approval action. We will request some additional data pertinent to concerns about possible valvulopathy with this drug as phase 4 commitments.

4.0 BIOPHARMACEUTICS

The issues in the original submission for the Office of Clinical Pharmacology (OCP) were: (1) the proposed dissolution specifications; (b) (4) and, (4) a possible valproic acid interaction.

(b) (4) In addition, we have reached agreement with the sponsor on an interim dissolution specification. We agreed that the valproate study is not needed.

All of these issues have now been addressed and OCP has recommended an approval action.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy reviews for SPD503 focused on two phase 3 studies in children and adolescents (ages 6-17), i.e., studies 301 and 304. Both studies were randomized, double-blind, parallel group, fixed-dose, multicenter (all US centers), and placebo-controlled, and all involved patients (ages 6-17) meeting DSM-IV-TR criteria for ADHD. For both studies, the primary endpoint was change from baseline to endpoint in ADHD-RS-IV.

-Study 301 was an 5-week, fixed-dose study (doses of 2, 3, and 4 mg/day). All 3 doses were highly statistically significantly superior to placebo, and there was a suggestion of a slight

numerical advantage to the 4 mg/day dose over the 2 lower doses (placebo-adjusted difference of about 10 units vs about 7.5 for the 2 lower doses).
-Study 304 was a 6-week, fixed-dose study (doses of 1, 2, 3, and 4 mg/day). All 4 doses were highly statistically significantly superior to placebo, and there was a suggestion of a slight numerical advantage for the 3 and 4 mg/day doses over the 2 lower doses (placebo-adjusted differences of about 7.9, 7.3, 5.4, and 6.8 for groups 4, 3, 2, and 1 mg, respectively).
-For both studies, analyses based on age suggested that the positive effects were coming almost entirely from children (ages 6-12) and not from adolescents (ages 13-17). Adolescents represented only about ¼ of the total subjects, however, even numerically the results were not suggestive of a drug effect in this subgroup. The sponsor has suggested that this difference likely resulted from inadequate plasma levels due to the higher body weights of adolescents, and they have proposed this explanation in labeling. I am inclined to accept this explanation.

In my view, studies 301 and 304 have established both the overall effectiveness of SPD503 in ADHD and evidence for dose response in a dose range of 1 to 4 mg/day. The sponsor has proposed adding the following language to labeling: "Clinically relevant improvements were observed beginning at doses in the range of 0.05-0.08 mg/kg/day. Efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg/day may provide additional benefit." This advice is based on an exploratory analyses, however, I think it is reasonably well-supported and I think encourages more rational dosing than dosing on simply a mg basis. An age analysis clearly suggests that the benefits of SPD503 were not demonstrated in adolescents, even though the studies were positive overall. I still think it is reasonable to permit a general claim of efficacy in this broad age range (6-17), along with a mention of this finding in labeling. With mg/kg dosing, I think adolescent patients can be effectively treated. The sponsor's proposed explanation based on likely inadequate exposure due to higher body weights in adolescents seems entirely reasonable to me. The sponsor has agreed to address this discrepancy in the efficacy findings as a phase 4 commitment. The sponsor has also committed to conducting a maintenance study post-approval.

5.2 Safety Data

The overall safety profile for guanfacine has been shown to be acceptable, and can be adequately characterized in labeling. There were two safety issues that needed resolution before taking a final action.

QT Prolongation

Although ECG monitoring was not ideal for assessing QT effects in the phase 3 trials, there did appear to be a signal for a modest QT effect. There were dose-related increases in QTcF ranging from 1 to 10 msec across the dose range of 1 to 4 mg/day (there was a 2 msec increase for placebo). No patients had QTcF values > 500 msec and no patients had cardiovascular events associated with prolongations in QTcF. Dr. Bhattaram from OCP reviewed the QT data and concluded that, for every 1 ng/mL increase in plasma guanfacine concentration, a 1 msec increase in QTc would be predicted. The sponsor reached a similar conclusion using a slightly different model. We asked the Division of Cardiorenal Products to consider these data, and they concluded that there is probably a modest QT effect, but recommended a thorough QT study to

provide a more definitive answer. It should be noted that there is no indication of a signal for postmarketing cases of TDP for immediate release guanfacine. (b) (4) However, our consultants recommended that certain precautions should be observed in using this drug, given the probable modest QT effect, e.g., avoidance in patients with congenital QT prolongation, and other risk factors, and also screening ECGs and serum potassium and magnesium. Consequently, in the draft labeling with our AE letter, we asked the sponsor to include these findings in the Warnings/Precautions section of labeling.

As part of the resubmission of this NDA, the sponsor included the results of a thorough QT study. Although the study failed to exclude a 10 msec increase in ΔΔQTc, the largest ΔΔQTcF values were oddly observed at 24 hours, at a time when plasma concentration would be exceedingly low. This finding suggested a possible alternative explanation for the effect, i.e., variation in autonomic tone related to discontinuation effects from the drug. We discussed these findings with the sponsor, and suggested alternative analyses. The sponsor has submitted these alternative analyses and we have reached agreement on how to characterize these unusual findings. We are in agreement that the findings are of limited clinical significance, and can be described in the Adverse Reactions section.

Possible Risk for Valvulopathy

A concern has been raised about a possible risk for valvulopathy associated with the use of guanfacine. This is based on a finding by Dr. Bryan Roth of UNC who conducted a broad screening of over 2200 compounds for 5HT2b agonism. He found that guanfacine ranked fairly high on this effect, although somewhat lower than 3 well-known valvulopathogens (norfenfluramine, pergolide, and cabergoline). 5HT2b agonism is thought to be the mechanism for this effect. Guanfacine IR has been marketed since 1986 for the treatment of hypertension, and in more recent years has also been used off-label for the treatment of ADHD. We have conducted an AERS search and have not found a single report of valvulopathy for this drug. We have also conducted a literature search and have found no reports of valvulopathy for this drug. This is somewhat reassuring, since reports emerged fairly quickly for the drugs believed to be valvulopathogens. We have discussed these findings with Drs. Temple, Ellis, and Stockbridge, and have decided to ask the sponsor to attempt to address this concern post-approval. Drs. Ellis and Stockbridge did not feel it would be useful to seek a replication of the assay, or to ask for human echocardiogram studies at this point. If this event does occur in association with guanfacine, it would have to be exceedingly uncommon, given that no cases have been observed, and, therefore, getting a few echos would not likely be productive. Rather, they felt that additional animal studies might be useful. We have discussed this matter with the sponsor, however, we still need to get agreement on certain preclinical studies regarding this concern and to have them submit as expedited reports any AERS cases of valvulopathy. In the meantime, we are in internal agreement that there is no justification for any labeling changes regarding this theoretical risk.

Conclusions Regarding Safety

In my view, SPD503 (guanfacine) is sufficiently safe to justify its use in treating ADHD. The safety concerns for this drug can be adequately addressed in labeling.

5.4 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have reached agreement on all issues except for the wording of the indication. (b) (4)

6.0 FOREIGN REGULATORY ACTIONS

SPD503 is still not approved anywhere at this time for the treatment of ADHD.

7.0 LABELING AND COMPLETE RESPONSE LETTER

7.1 Labeling

We have included our proposed label in the CR letter.

7.2 Phase 4 Commitments

The following are the commitments we feel are needed (not include in CR letter):

-Longer-term efficacy study
-Additional efficacy data in adolescents
-Controlled trial to assess the safety and efficacy of guanfacine as adjunctive therapy to stimulant therapy (this study is ongoing)
-Preclinical study involving concomitant use of stimulants and guanfacine (this can be done as part of juvenile animal study)
-Preclinical stimulant/guanfacine combination study in juvenile rats, including mating and fertility data in guanfacine monotherapy arm
-Valvulopathy:
    -Additional preclinical data regarding this concern
    -Expedited reporting of any spontaneous reports of valvulopathy
-Re-evaluation of dissolution testing within the first year of marketing

We have obtained agreement from the sponsor on all of these, except for the special nonclinical studies regarding valvulopathy

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Shire has submitted sufficient data to support the conclusion that SPD503 is effective and acceptably safe in the treatment of ADHD. We have not, however, reached agreement on final labeling and phase 4 commitments. Thus, I will issue a CR letter with our proposed labeling.

cc:
Orig NDA 22-037
HFD-130
HFD-130/TLaughren/MMathis/RLevin/SChang

DOC: Guanfacine_Laughren_CR Memo.doc

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22037	ORIG 1	SHIRE DEVELOPMENT INC	INTUNIV

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
07/28/2009