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: September 1, 2009

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

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

TO: File NDA 22-037
[Note: This final approval memo should be filed with the 7-28-09 response to our 7-27-09 complete response letter for this NDA. The reader is referred to my earlier two memos dated 6-19-07 and 7-27-09 for background on relevant information regarding all findings and events preceding the 7-28-09 response.]

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 and a complete response (CR) letter on 7-27-09. The CR letter included draft labeling, a request to submit draft carton and container labeling, and proposed dissolution specifications. In addition, at the time of the 7-27-09 CR action, we had reached agreement on all postmarketing requirements and commitments with the exception of an animal study to address concerns about a possible risk of valvulopathy.

2.0 RESOLUTION OF REMAINING ISSUES

These remaining issues have now all been resolved:

-Labeling: The main issue for resolution was how to characterize the new claim in the Indications and Usage section of labeling. After some discussion, we agreed on a broad claim for the treatment of ADHD, but with qualifying information specifying what studies were the basis for the claim. Thus, we now have agreement on final labeling.

-Carton and Container Labeling: We have reached agreement with the sponsor on carton and container labeling.

-Dissolution Specifications: We have reached agreement on dissolution specifications.

-PMR for Animal Study to Explore for Valvulopathy: We have reached agreement on an appropriate cardiac toxicity study in rats.

3.0 CONCLUSIONS AND RECOMMENDATIONS

Shire has now submitted sufficient data to support the conclusion that SPD503 is effective and acceptably safe in the treatment of ADHD. We have reached agreement on final labeling, on phase 4 commitments, on carton and container labeling, and on a rat cardiac toxicity study. Thus, I will issue an approval letter with our mutually agreed upon labeling.

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

DOC: Guanfacine_Laughren_AP 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
09/01/2009