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APPLICATION NUMBER:

022063Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-063

Shire Development
Attention: Zohra Lomri
Associate Director, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Mrs. Lomri:

Please refer to your new drug application (NDA) dated and received July 21, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (mixed salts of a single entity amphetamine) 12.5 mg, and 25 mg Extended Release Capsules.

We acknowledge receipt of your submissions dated August 29, 2006, September 7, 18, 29, 2006, October 9, 2006, November 9, 14, 17, 29, 2006, January 22, 31, 2007, March 7, 2007 and April 10 and 27, 2007.

This new drug application provides for the use of (b) (4) (mixed salts of a single entity amphetamine) 12.5 mg, and 25 mg Extended Release Capsules for the treatment of attention deficit hyperactive disorder (ADHD).

We have completed our review of this application, as submitted, 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:

- We find your proposed dissolution methodology acceptable. However, we request that the specifications be changed to allow a (b) (4) % range.

- Please perform dissolution studies for all (b) (4) strengths using the current dissolution conditions with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media.

- These studies must be completed and submitted to this NDA with your complete response to this action letter.

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:	50 RPM
Media:	Media 1: pH 1.1 ± 0.1, Dilute HCl Media 2: pH 6.0 ± 0.1, Phosphate Buffer Media 3: pH 7.5 ± 0.1, Phosphate Buffer
Temperature:	37.0°C ± 0.5°C
Dissolution Volume:	750mL Dilute HCl for the first 2 hours 950mL pH 6.0 Phosphate Buffer for the 3rd hour 1000mL pH 7.5 Phosphate Buffer for the remainder

Specification:

Time	Percent Dissolved
2	(b) (4)
3	
10	

Expiry

Based upon your submitted stability data, we are granting a 24 month expiry for all strengths of (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).

Additionally, please note that we have not incorporated your proposed 37.5 mg and 50 mg strengths since there was no additional efficacy at these higher doses, and there were additional adverse events associated with these higher doses.

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 (b) (4), 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 July 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. Currently, there is an approved extended release formulation of (b) (4) named Adderall XR, which is also marketed by you. This product is marketed as 5 mg, 10 mg

15 mg, 20 mg, 25 mg, and 30 mg capsules to adults and pediatric patients. Your proposed product, (b) (4) contains (b) (4) mixed amphetamine salts found in Adderall XR, and is equivalent to an Adderall XR plus a follow-up dose of Adderall. (b) (4) duration of action is 16 hours and the pharmacokinetic profile is equivalent to dosing with Adderall XR followed 8 hours later by the immediate-release formulation, Adderall.

The introduction of this proposed formulation in the marketplace is potentially problematic and may lead to errors because it will be difficult for practitioners to readily discern these different formulations. Additionally, (b) (4) will not have a modifier to identify it as an extended release product. Therefore, practitioners will look to its established name for differences between this and Adderall XR. However, Adderall and (b) (4) will have the same established name. Moreover, they have an overlapping dose at 25 mg. DMETS is concerned that both patients and health care practitioners will not be aware of the formulation differences because the products contain the same active ingredients and have an overlapping strength and frequency of administration. Furthermore, indicators will not be available to clue practitioners to the fact that the products are different and they cannot be substituted for one another. This will become even more problematic when the product becomes available as a generic equivalent.

Therefore, we ask that you create and implement a plan for the education of healthcare professionals and consumers about the difference between (b) (4) and the available Adderall formulations. Advice from practicing healthcare providers should be sought on how to label and educate to adequately address the fact that the products are different despite having the same active ingredients, established name, dose, and dosing intervals. This plan should be executed for the life-cycle of the product.

2. Ensure that the product labels and labeling are not similar to and do not overlap with the existing color scheme of Adderall XR product labels and labeling.

B. CONTAINER LABEL

1. It appears, from the all capital presentation and bolded font of the proprietary name, that it is more than twice the size of the established name. Although the size of the established name may meet the regulatory requirements, the prominent presentation of the proprietary name makes the established name appear smaller than ½ of the size of the proprietary name. We recommend increasing the prominence of the established name.

2. Postmarketing experience has shown that medication errors have occurred due to confusion of the net quantity for the product strength if they are in close proximity to each other. Thus, we request relocation of the net quantity statement so that it is not in close proximity to product strength.

3. We note that the font color used for the text of the net quantity statement is the same color used for the strength. Post-marketing error reports describe confusion of the strength and net quantity when they appear with a similar color to one another. DMETS

recommends that the color of the net quantity be revised so that it is not presented in the same color as the strength.

C. INSERT LABELING

1. We recommend that you delete the use of trailing zeros corresponding to the strength of each active ingredient in the 'Description' section of the package insert labeling. 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 listed as one of these dangerous abbreviations. Thus, we request that the Divisions not approve or use trailing zeros in their labels and labeling because the labeling habits carry over to prescribing habits. If the strength is prescribed with trailing zeros as seen in the labeling, this provides an opportunity for error. The decimal point may not be readily apparent and lead to a ten-fold dosing error.

   Additionally, the use of terminal zeroes in the expression of strength or volume is not in accordance with the USP General Notices (page 10) of 2004, 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). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list trailing zeros on their dangerous abbreviations and dose designations list.

2. Since patients may need counseling on alternative administration of this product (i.e., sprinkle the entire contents on applesauce), DMETS recommends that you include section 17 (Patient Counseling Information) so that it can be provided to patients.

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."

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