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RESEARCH**

APPLICATION NUMBER:

207488Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	207844
Applicant Name	Amedra Pharmaceuticals LLC
Date of Submission	August 11, 2014
PDUFA Goal Date	June 11, 2015
Established (USAN) Name	Albendazole
Dosage Forms / Strength	Chewable Tablets, 200 mg
Proposed Indications	<ol style="list-style-type: none"> 1. Parenchymal neurocysticercosis 2. Cystic hydatid disease of liver, lung and peritoneum
Recommended Action:	Approval

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Wendelyn Schmidt PhD
Chemistry Manufacturing and Controls Review	Caroline Strasinger PhD
Quality Biopharmaceutics Review	Salaheldin Hamed PhD
Cross-Discipline Team Leader Review	Angelica Dorantes PhD
Medical Officer Review	Kimberly Martin DO MPH
Statistical Review	Cheryl Dixon PhD
Product Quality Microbiology Review	Erica Pfeiler PhD
Clinical Microbiology Review	Lynette Berkeley PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Division of Medication Error Prevention and Analysis (DMEPA)	Danielle Neupauer, RPh, Tingting Gao, Pharm D
Office of Prescription Drug Promotion (OPDP)	Puja Shah Pharm D

1.0 Introduction

NDA 207844, Albendazole 200 mg chewable tablets was submitted by Amedra Pharmaceuticals LLC on August 11, 2014. Albenza (albendazole) tablets (NDA 20666) is approved for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, *Taenia solium*, and for the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by larval form of the dog tapeworm, *Echinococcus granulosus*.

2.0 Background

Albenza® (albendazole), 200 mg film-coated tablet, was approved under NDA 20666 on June 11, 1996. The holder of the NDA was SmithKline Beecham, now GlaxoSmithKline (GSK). On November 1, 2012, Amedra Pharmaceuticals LLC acquired rights from GSK for distribution of the product in the United States and GSK retained rights for ex-US marketing and distribution. GSK continues to manufacture the drug for Amedra Pharmaceuticals and the companies maintain a Safety Data Exchange Agreement. GSK maintains the albendazole global safety database. Both indications approved under NDA 20666 were granted orphan drug designation in January 1996.

On February 21, 2007, GSK had submitted a Changes Being Effected labeling supplement to add safety language to the Precautions, Information for Patients section and to the Dosage and Administration section regarding difficulty with swallowing the tablet based on five reported pediatric cases of asphyxia and/or choking with administration of Albenza. The labeling supplement was approved on August 20, 2007. The product label states that in young children, the tablets should be crushed or chewed and swallowed with a drink of water.

Amedra Pharmaceuticals LLC submitted this NDA for a 200 mg chewable tablet to provide better palatability for patients who have difficulty swallowing tablets, including young children.

The review team has completed their reviews of this application. For a detailed discussion of NDA 207884, please refer to discipline specific reviews and the Cross-Discipline Team Leader (CDTL) review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Caroline Strasinger, PhD, and the Product Quality Microbiology reviewer is Erica Pfeiller, PhD.

Drug substance information is referenced to DMF (b) (4). The Applicant has provided a letter of authorization to reference the DMF. The drug substance for this NDA is the same as in NDA 20666. In a review dated September 23, 2014, Sung Kim, PhD, noted that the DMF was adequate to support NDA 20666 (b) (4). No additional amendments have been added to the DMF since the last review. Sixty months of long-term and 6 months accelerated stability data were provided in the NDA. The data support a retest period of (b) (4).

The drug product is a round, mottled pink, concave chewable 200 mg tablet debossed with the product code “ap” above “551” on one side and plain on the other side. The tablets are manufactured, packaged, and release and stability tested at (b) (4) and the final release of the drug product is the responsibility of Amedra Pharmaceuticals LLC. The quality of the drug product is controlled by tests for appearance, identification, assay, related substances, content uniformity, dissolution, and residual moisture.

Albenza chewable tablets, 200 mg, will be packaged in (b) (4) or (b) (4) blisters with either peel push, or push through foil lidding. Expiration dating of 24 months is supported by 12 months stability data for (b) (4) blisters.

The Applicant proposed a waiver of microbial limits testing for product release, and provided information related to the product manufacturing, microbiological specifications for excipients, and finished product (b) (4) to support this proposal. Acceptance criteria were provided for the drug product excipients, and all were generally within limits described in USP <1111> for nonaqueous preparations for oral use. The Applicant has not performed microbial limits testing on the product to date, but commits to performing tests on upcoming process validation batches and providing the results in an annual report. Additionally, the Applicant committed to performing microbial limits at the initial stability time point for commercial batches. Dr. Pfeiler found the Applicant’s proposal to waive microbial limits testing for product release acceptable.

The Office of Compliance has issued an overall recommendation of “Acceptable” for this NDA.

Based on overall assessment of the CMC information submitted in the NDA, Dr. Strasinger concludes that sufficient information has been provided to assure identity, strength, purity, and quality of the drug product and recommends approval of the NDA. I agree with her assessment.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Wendelyn Schmidt, PhD. No new toxicology data were submitted in this NDA. Dr. Schmidt recommends approval of the NDA from a pharmacology/toxicology perspective.

5.0 Biopharmaceutics

The Biopharmaceutics reviewer for this NDA is Salaheldin Hamed, PhD. Data to support this NDA come from the following studies:

Study (b)(4)/13/186: An open label, randomized, three-period, three-sequence, single dose, crossover bioequivalence study in healthy male and female subjects under fasted conditions. The test product was Albenza Chewable Tablets, 200 mg (2 tablets for a total dose of 400 mg), Lot# B130391 and the reference product was Albenza Tablets, 200 mg (2 tablets for a total dose of 400 mg), Lot# 2A002. The products were administered orally as a single dose. The geometric mean ratio and the 90% confidence interval (CI) for the pharmacokinetic parameters, AUC_{0-72} , AUC_{inf} , and C_{max} for albendazole and its metabolite, albendazole sulfoxide, were within the acceptable 80%-125% bioequivalence range.

Study (b)(4)/13/187: An open label, randomized, three-period, three-sequence, single dose, crossover study in healthy male and female subjects under fed conditions. The test product was Albenza Chewable Tablets, 200 mg (2 tablets for a total dose of 400 mg), Lot# B130391. The reference product was Albenza Tablets, 200 mg (2 tablets for a total dose of 400 mg), Lot# 2A002. The products were administered orally as a single dose. The geometric mean ratio and the 90% CI for AUC_{0-72} , AUC_{inf} , and C_{max} for albendazole and the metabolite, albendazole sulfoxide were found to be within the acceptable 80%-125% bioequivalence range.

The dissolution method and acceptance criterion originally proposed by the Applicant was unacceptable. Based upon an information request from the Agency, dated October 16, 2014, the Applicant revised the method and the criterion and the following was acceptable to the Biopharmaceutics reviewer, Dr. Hamed:

Dissolution Method: USP Apparatus II, 50 Rpm, 900 mL 0.1 N H at 37°C

Acceptance Criterion: $Q = \frac{(b)(4)}{(4)}\%$ at 30 min

Data from two additional pilot bioequivalence studies, one each in fed and fasted state were included in the NDA. Dr. Hamed did not review the data from these studies as they were not considered necessary to support the bioequivalence of the new formulation. Safety data from these two studies were reviewed by Dr. Martin to support the safety of the chewable tablets.

Dr. Hamed and the CDTL, Dr. Dorantes recommend approval of the NDA and I agree with their recommendation.

6.0 Clinical Microbiology

Lynette Berkeley, PhD, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. Labeling recommendations have been incorporated in the Microbiology section of the package insert.

7.0 Clinical Pharmacology

Dakshina Chilukuri, PhD, is the clinical pharmacology reviewer for this application. Dr. Chilukuri notes that the application is acceptable from a clinical pharmacology perspective. No new clinical pharmacology information was submitted in this NDA. Dr. Chilukuri's recommendations for labeling have been incorporated.

8.0 Clinical Efficacy/Safety

Kimberly Martin, DO, MPH is the clinical reviewer for this application. No new efficacy data were submitted in this NDA. Safety of the chewable tablet was assessed in four bioequivalence studies. A total of 369 subjects received at least one dose (400 mg) of study drug and were included in the safety analysis.

The majority of subjects were Asian males and ranged in age from 18-45 years. No deaths or Serious Adverse Events (SAEs) were reported. Nineteen (5.1%) subjects reported a total of 20 non-serious Treatment Emergent Adverse Events (TEAEs); 15 subjects (4.1%) discontinued due to TEAEs, 10 receiving the chewable tablet and five receiving the referenced product. The TEAEs reported included vomiting, fever and dizziness. Non-serious TEAEs were reported in 19 subjects (5.1%) 10 with the chewable tablets, five with the referenced product and five after receiving both drugs. All TEAEs were assessed as either mild or moderate in severity. The most common TEAE that was considered possibly or probably related to study drug and that led to discontinuation from the study was mild vomiting (9, 2.4%). There were five reports of laboratory TEAEs, including three reports of low platelet count, 1 report of low white blood cell count and 1 report of low hemoglobin levels. All five AEs occurred after administration of both drug products and were reported as resolved at the conclusion of the study. All reported safety and laboratory AEs are included in the current package insert.

The Applicant also performed a search of the GSK/Amedra Pharmaceuticals safety database for albendazole, a review of the scientific literature and a search of the FDA Adverse Events Reporting System (FAERS) for albendazole-related safety reports. In the literature review, 540 AEs were identified; 22 reports (4%) of unexpected SAEs were all identified from foreign literature and all occurred once with the exception of dystonia, for which there were two events. A search of FAERS from 2004 to 2014 identified 2,902 AEs; 98% were reported as expedited

(15-Day) events. The most commonly reported events ($\geq 2\%$) by preferred terms were asthenia (87 events, 3%), vomiting (81 events, 2.8%), pyrexia (73 events, 2.5%) and headache (70 events, 2.4%). With the exception of asthenia, all the commonly reported AEs are included in the package insert. Of the expedited events, the most frequently reported ($\geq 1\%$) AEs included asthenia, vomiting, pyrexia, headache, diarrhea, dizziness, vision blurred, somnolence, convulsion, abdominal pain, rhabdomyolysis, and Stevens Johnson Syndrome. Of these AEs, asthenia, diarrhea, vision blurred, somnolence, and rhabdomyolysis are not described in the current package insert. Based on this safety review, the Applicant proposed the addition of asthenia, diarrhea, vision blurred, somnolence and rhabdomyolysis to the Adverse Reactions section of the package insert. In addition, the AE of convulsion was added by the Agency after review of FAERS which identified 29 (29/2902, 1%) reports of convulsions.

Dr. Martin's recommendations for labeling have been incorporated. Dr. Martin recommends approval of the NDA. I agree with her assessment.

Cheryl Dixon, PhD, is the statistics reviewer for this NDA. Dr. Dixon notes that no new clinical data were submitted and that the proposed labeling changes are acceptable.

9.0 Labeling

In addition to updating information regarding the new formulation, labeling was updated to the Physician Labeling Rule (PLR) format. Labeling recommendations from all disciplines were incorporated in the final labeling. Danielle Neupauer, RPh, from the Division of Medication Error Prevention and Analysis performed a labeling review and her recommendations for labeling revisions have been incorporated. Labeling recommendations from Puja Shah, Pharm D, from the Office of Prescription Drug Promotion have also been incorporated in labeling.

10.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), 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 the requirement is waived, deferred or inapplicable. Per a communication from the Office of Orphan Products Development, the Orphan Drug

designation granted for both indications were transferred from GSK to Amedra Pharmaceuticals on November 5, 2014.¹ Thus, no pediatric studies are required.

11.0 Other Regulatory Issues

The Office of Scientific Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of the bioequivalence Study (b) (4)-13-187 conducted by (b) (4). Data from this study were found to be acceptable and OSIS recommends that the data be used for Agency review. This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC), as there were no issues requiring input from the AIDAC.

12.0 Recommended Regulatory Action

I agree with the assessment made by the review team that NDA 207844, Albenza (albendazole) chewable tablets, 200 mg be approved. The Applicant has provided adequate information to demonstrate the bioequivalence of the chewable tablets to the approved Albenza (albendazole) tablets (NDA 20666). Safety information has been incorporated in appropriate sections of labeling. I recommend approval of this NDA.

¹ http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=094295

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/s/

SUMATHI NAMBIAR
06/11/2015