CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207844Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Date	February 19, 2015
From	Kimberly C. Martin, D.O., MPH
Subject	Clinical Review
NDA/BLA # **Supplement#**	NDA 207844
Applicant	Amedra Pharmaceuticals, LLC
Date of Submission	June 19, 2014
PDUFA Goal Date	June 11, 2015
Proprietary Name / Established (USAN) names	Albenza®
Dosage forms / Strength	200 mg chewable tablet
Proposed Indication(s)	1. Parenchymal Neurocysticercosis 2. Cystic hydatid disease of liver, lung and peritoneum
Recommended:	Approval

1. Introduction

Albendazole is an anthelmintic drug which 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 the larval form of the dog tapeworm, *Echinococcus granulosus*.

2. Background

Albenza ® (albendazole) was approved on June 11, 1996 under NDA 20666. The current formulation is a 200 mg coated tablet. Amedra Pharmaceuticals acquired rights from the initial NDA holder, GlaxoSmithKline (GSK), on November 1, 2012 for distribution of the product in the United States while GSK retained ex-US marketing and distribution rights. GSK continues to manufacture the drug for Amedra Pharmaceuticals and the companies maintain a Safety Data Exchange Agreement.

Because of five reported pediatric cases of asphyxia and or choking with administration of the drug, the Dosage and Administration portion of the product insert was updated by GSK in 2007. The package insert now states that in children, tablets should be crushed or chewed and swallowed with a drink of water. In order to provide better palatability for children or patients with swallowing difficulties, Amedra Pharmaceuticals has submitted this NDA for a 200mg chewable tablet.

This NDA is submitted as a 505 (b)(1) application and is based on four healthy volunteer bioequivalence (BE) studies completed by Amedra Pharmaceuticals. The submission relies

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on investigations that were conducted by GSK but obtained by the applicant through a right of reference. Therefore, no other pharmacology/toxicology, clinical pharmacology, microbiology or clinical efficacy studies were performed by the Applicant. With the original NDA submission, GSK was granted Orphan Drug Designation for both indications but transferred this designation to Amedra Pharmaceuticals on November 5, 2014 therefore pediatric studies are not required.

3. CMC

The primary CMC review was completed by Caroline Strasinger, Ph.D., please see her review for full CMC details.

Albendazole ($C_{12}H_{15}N_3O_2S$) is methyl 5-(propylthio)-2-benzimidazolecarbamate. The drug substance is a white to faintly yellowish powder. The currently marketed product is a 200 mg white to off-white, circular, biconvex, bevel-edged film coated, tablet. The proposed 200 mg chewable tablet is a round, mottled pink, concave tablet. The excipients used in the proposed 200mg chewable drug product were chosen to yield a dissolution profile similar to the original coated tablet and include additions for appearance and palatability. The chewable tablet dissolution profile was reviewed by the biopharmaceutics reviewer and found to be acceptable and similar to the coated tablet.

Inspections of the analytical and clinical sites were performed by the Office of Scientific Investigations (OSI) and are pending at the time of this review.

Dr. Strasinger did not identify CMC deficiencies, and pending OSI review, recommends approval.

4. Nonclinical Pharmacology/Toxicology

No further Nonclinical Pharmacology/Toxicology studies were submitted other than what is already included in the current Albenza® package insert.

5. Clinical Pharmacology/Biopharmaceutics

The major focus of this submission was demonstrating bioequivalence of the new 200 mg chewable tablet to the approved 200mg coated tablet. The quality biopharmaceutics review was performed by Salaheldin Hamed, Ph.D., in the Office of New Drug Quality Assessment (ONDQA).

Four BE studies, two pilot (fasted, (b) (4)/13/052 and fed, (b) (4)/13/053) and two pivotal (fasted, (b) (4)/13/186 and fed, (b) (4)/13/187) were completed in a total of 372 male and female healthy volunteers. The two pilot studies enrolled a total of 120 subjects and the two pivotal studies enrolled a total of 252 subjects. All subjects received two tablets for a total dose of 400mg. All

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four protocols were randomized, open label, balanced, two-treatment, three-period, single dose, reference replicated, crossover bioequivalence studies. A total of 186 subjects received test (chewable), and reference product (coated tablet) under fed conditions and a total of 186 subjects received test and reference product under fasted conditions. Bioequivalence analyses were performed by the Applicant using data from 333 subjects who had received both the test and the reference products under fasted (n = 168) and fed (n = 165) conditions. The ONDQA assessment was based on the two pivotal studies and included the bioequivalence parameters of AUC_{0-72}, AUC_{inf}, and C_{max} for the test and reference products. The secondary parameters T_{max}, K_{el}, and half-life were also analyzed.

In both the fasted and fed studies, the order of administration was according to a randomization schedule, with a 7-day washout period between each of the three treatment periods. Blood samples were collected at pre-dose (0 hours) and at intervals over 72 hours (0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6, 8, 10, 12, 16, 18, 24, 48, and 72). The analysis of plasma concentrations of albendazole and its metabolite albendazole sulfoxide were done by a validated LC-MS/MS analytical method.

The biopharmaceutical review found that the studies were executed using acceptable protocols for demonstrating BE (sample size, dosing schedule, washout period, statistical method). There were no observed protocol deviations that could impact study outcomes. Justifications provided for excluding any subject data from the PK analysis were found to be acceptable. In the fasted and fed studies, sequence or period effects were not observed. The geometric mean ratio, along with the 90% confidence interval, of the PK parameters (AUC_{0-72}, AUC_{inf}, and C_{max}) for albendazole and the metabolite, albendazole sulfoxide, were within the acceptance range of 80%-125% and the ONDQA reviewer recommended approval based on BE parameters.

6. Clinical Microbiology

No further Clinical Microbiology studies were submitted.

7. Clinical/Statistical- Efficacy

No efficacy data was obtained in these BE studies.

8. Safety

A total of 369 subjects received at least one dose of study drug and were included in the pooled safety profile. The majority of subjects were Asian males aged 18-45. No deaths or SAEs were reported. Fifteen subjects (15/369, 4.1%) discontinued from the study due to Treatment Emergent Adverse Events (TEAE) such as vomiting, fever and dizziness. Ten of the discontinued subjects received test product and 5 of them received reference product.

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Nineteen subjects (19/369, 5.1%) reported a total of 20 non-serious TEAEs during the conduct of these studies. Of these 20 TEAEs, 10 were reported after receiving the test drug, 5 after receiving the reference drug and 5 after receiving both drugs making the attribution to test or reference drug not possible. All of the TEAEs were assessed as either mild or moderate in severity. Seventeen of the TEAEs (17/20, 85%) were assessed as possibly or probably related to study drug and four were assessed as not related. 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%] subjects). Of the AEs reported, 5 were laboratory AEs. These included 3 episodes of low platelet count, 1 report of low white blood cell count (WBC) and 1 report of low hemoglobin levels. All TEAEs were reported as resolved at the conclusion of the study and all of the safety and laboratory AEs are present in the current product insert.

In addition to reported laboratory AEs, laboratory values of interest were investigated for all subjects including WBC count, platelet count, hemoglobin, creatinine, AST and ALT. No major unexpected abnormalities were noted in the laboratory values.

With this submission, the Applicant completed a search of the GSK/Amedra Pharmaceuticals albendazole safety database, the scientific literature for reported albendazole adverse events and queried the FDA Adverse Events Reporting System (FAERS). In the albendazole safety database, 540 reportable albendazole AEs were identified with 22 reports (4%) of unexpected SAEs originating from the literature. All of these SAEs originated from foreign literature and all had a single occurrence with the exception of *dystonia*, for which there were two events. A search of FAERS reports from 2004 to the first quarter of 2014 identified 2,902 AEs. Of these, 98% were reported as expedited (15-Day) events. The most commonly reported events (≥ 2%) by preferred terms were *asthenia* (87 events, 3%), *vomiting* (81 events, 2.8%), *pyrexia* (73 events, 2.5%) and h*eadache* (70 events, 2.4%). None of the AEs were reported with an occurrence of greater than 3%. All of the most common AEs are described in the current Albenza® package insert with the exception of *asthenia*. Of the expedited events, the most frequently reported (≥ 1%) included *asthenia, vomiting, pyrexia, headache, diarrhea, dizziness, vision blurred, somnolence, convulsion, abdominal pain, rhabdomyolysis*, and *Stevens Johnson Syndrome*. These most commonly reported 15-Day AEs are described in the current Albenza® package insert with the exception of *asthenia, diarrhea (*50 events, 1.7%*), vision blurred* (32 events, 1.1%), *somnolence* (30 events,1.1%), and *rhabdomyolysis (28 events, 1%)*. Based on this safety review, The Applicant recommends addition of the terms *asthenia*, *diarrhea, vision blurred, somnolence and rhabdomyolysis*.

Medical Officer Comment: No major unexpected safety signals were noted in these BE studies. Numerically more subjects had adverse events after being dispensed the test product although the small number of AEs precludes any valid comparisons. The safety update performed by the Applicant was thorough and included an internal, scientific literature and FAERS review. The safety update identified multiple events to be added to the package insert. This literature review was replicated and no other reports were found which in the opinion of this reviewer should be added to the product insert.

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9. Pediatrics

Pediatric studies were not required with this submission because of the product's Orphan Designation.

10. Labeling

Along with conversion of the package insert to the PLR standard, this labeling revision included the addition of information pertaining to the chewable tablet BE studies and adverse reaction terms in Section 6.2 Postmarketing Experience. These terms include *asthenia*, *diarrhea, vision blurred, somnolence, rhabdomyolysis and convulsion*. The addition of the term *convulsion* was added by the Agency after review of the submitted FAERS query which noted 29 (29/2902, 1%) reports of *convulsion*. Although the current package insert references seizures in subjects with neurocysticercosis in Section 5 Warnings and Precautions, the term is not present in the current Adverse Reactions or Postmarketing Experience sections.

11. Recommendations/Risk Benefit Assessment

Based on demonstration of bioequivalence to the currently approved 200mg coated tablet, this 200mg chewable Albenza® tablet NDA is recommended for approval pending finalization of the OSI inspection report. Safety events including laboratory adverse events reported in the four BE studies were expected and all events are included in the current package insert. The safety update including a search of the scientific literature and FAERS reports was well performed and identified 6 previously unlabeled adverse reactions to be added to the package insert.

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/s/

KIMBERLY C MARTIN
02/20/2015

HALA H SHAMSUDDIN
02/21/2015

CLINICAL FILING CHECKLIST FOR NDA

NDA Number: 207844 **Applicant: Amedra Pharmaceuticals LLC** **Stamp Date: June 19, 2014**

Drug Name: Albenza **NDA Type: 3**

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			Electronic clinical datasets not provided
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			505 (b)(2)- only Quality and Clinical information submitted. No micro or pre-clinical sections
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505 (b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Albendazole (Albenza)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	x			Purpose of the submission- BE studies
15.	Describe the scientific bridge (e.g., BA/BE studies)	x			Purpose of the submission- BE studies
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:			x	BE study

File name: 5_Clinical Filing Checklist for NDA_207844

Reference ID: 3606284

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
	Study Title: Sample Size: Arms: Location in submission:				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	BE study
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	BE study
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	BE study
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	BE study
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		x		Clinical BE data submitted but no safety (literature) update included
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	BE study
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		x		No safety (literature) update included. After initial request, 5 PADERS were submitted but found to be inadequate. Will request a full literature search be submitted
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

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CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		x		Will request
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	Safety updated needed, see comment #23
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	No pre-submission discussion
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Not required because of orphan designation
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	505(b)(2)
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	BE study
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Tabular listing of AEs and laboratory data submitted which does allow review but no electronic clinical datasets provided therefore will request for ease of review
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	No pre-submission discussion
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	BE study only
37.	Are all datasets to support the critical safety analyses available and complete?	x			Tabular listing of AEs and laboratory data submitted but no electronic clinical datasets provided- will

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
					request
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	BE study only
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	No pre-submission discussion
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. The 5 PADER files you have submitted do not suffice as a safety update. Please perform a full scientific literature search including a search of FAERS reports and submit as a safety update. This information should be concisely summarized and evaluable. If new safety event information is found, please include in your updated product label.

2. Please submit XPT transport files for clinical AE and laboratory datasets.

3. Please submit a coding dictionary. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Kimberly Martin, D.O. 7/29/14
Reviewing Medical Officer Date

Shrimant Mishra, M.D.
Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_207844

Reference ID: 3606284

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

/s/

KIMBERLY C MARTIN
08/07/2014

SHRIMANT MISHRA
08/07/2014