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APPLICATION NUMBER:

207844Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date:	April 23, 2015
From:	Angelica Dorantes, Ph.D. Acting Biopharmaceutics Branch Chief Division of Biopharmaceutics, ONDP, OPQ
Subject:	Cross-Discipline Team Leader Review
NDA:	NDA 207844
Type of Submission:	505(b)(2)
Applicant:	Amendra Pharmaceuticals LLC
Date of Submission:	June 19, 2014
PDUFA Goal Date:	June 11, 2015
Proprietary Name: Established (USAN) name:	Albenza® Albendazole
Dosage forms / Strength	Immediate Release Oral Chewable Tablets / 200 mg
Proposed Indication(s):	Albendazole is an anthelmintic drug indicated for: <ul style="list-style-type: none"> • Treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, <i>Taenia solium</i> • Treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of the dog tapeworm, <i>Echinococcus granulosus</i>.
Recommendation:	APPROVAL is recommended with labeling changes

This secondary CDTL review is based on the primary reviews/memos from:

DICIPLINE	PRIMARY REVIEWER	FINAL REVIEW DATE
Non-Clinical (Pharmacology-Toxicology)	WENDELYN J. SCHMIDT, PhD	No final review in DARRTS
Quality-CMC	CAROLINE STRASINGER, PhD	3/26/2014
Quality-Microbiology	ERIKA A. PFEILER, PhD	11/13/2014
Biopharmaceutics	SALAHELDIN S. HAMED, PhD	4/23/2015
Biometrics	CHERYL A. DIXON, PhD	4/14/2015
Clinical Pharmacology	DAKSHINA M. CHILUKURI, PhD	4/21/2015
Clinical	KIMBERLY C. MARTIN, D.O., MPH	2/20/2015
Clinical Microbiology	LYNETTE Y. BERKELEY, Ph.D.	10/21/14 and 12/01/2014
Medication Error Prevention and Analysis	DANIELLE NEUPAUER, RPh, and TINGTING N. GAO, Pharm.D	10/7/2014 (proprietary name) 10/17/14, 10/21/2014, 11/21/2014 (labels & labeling)
Prescription Drug Promotion	PUJA J. SHAH	2/24/2015
Regulatory Project Manager	GREGORY F. DIBERNARDO	4/16/2015

Cross Discipline Team Leader Review

1. Introduction

On June 19, 2014, the Applicant, Amendra Pharmaceuticals LLC., submitted NDA 207-844 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, seeking authorization to market Albenza® (albendazole), 200 mg Chewable Tablets.

Albenza® (albendazole), 200 mg Tablets, approved under NDA 20-666 on June 11, 1996, is the Listed Drug Product being used as the reference product for the supporting bioequivalence studies. Amendra Pharmaceuticals LLC is also the holder of the Listed Drug Product.

It is noted that the initial holder of NDA 207-844 was GlaxoSmithKline (GSK) and Amendra Pharmaceuticals acquired the NDA's rights 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 Amendra Pharmaceuticals and the companies maintain a Safety Data Exchange Agreement. It is also noted that an Orphan Drug Designation status was granted to NDA 20-666 on January 17 & 18, 1996 for both indications, but GSK transferred this designation to Amendra Pharmaceuticals on November 5, 2014.

2. Background

Albendazole is a well-known broad spectrum anthelmintic drug and is indicated 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*. Dosing will vary depending upon which parasitic infection is being treated. In general, an adult patient is administered 400 mg twice daily with meals for 8-30 days. Albendazole is contraindicated in patients with known hypersensitivity to benzimidazole class of compounds.

The mechanism of action of albendazole is to bind to the colchicine-sensitive site of β -tubulin inhibiting their polymerization into microtubules. The decrease in microtubules in the intestinal cells of the parasites decreases their absorptive function, especially the uptake of glucose by the adult and larval forms of the parasites, and also depletes glycogen storage. Insufficient glucose results in insufficient energy for the production of adenosine triphosphate (ATP) and the parasite eventually dies.

In this NDA the Applicant is seeking approval of Albenza® (albendazole) Chewable Tablets, 200 mg. The Applicant developed the chewable tablet formulation presented in this NDA, to provide a more desirable alternative formulation to the approved Albenza® 200 mg film coated tablets which present a potential choking hazard for those patients who have difficulty swallowing tablets, particularly young children.

Supporting Studies

The basis of approval of this NDA for Albenza® Chewable Tablets are two pivotal bioequivalence (BE) studies under fed and fasted conditions. The application did not utilize any published literature as a source of clinical data. The Applicant submitted data from two pilot and two pivotal BE studies. These studies are summarized in the table below.

Summary of Clinical Bioequivalence Studies

Study Number	Study Type	Number of Enrolled Subjects	Study Start	Study Completion
(b) (4) /13/052	Pilot; fasted	60	29 March 2013	17 May 2013
(b) (4) /13/053	Pilot; fed	60	09 April 2013	18 May 2013
(b) (4) /13/186	Pivotal; fasted	126	04 October 2013	08 November 2013
(b) (4) /13/187	Pivotal; fed	126	22 October 2013	02 December 2013

1. **Pilot BE Study No. (b) (4) /13/052:** A randomized, open label, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover, bioequivalence study of Albendazole Chewable Tablets, 200 mg of Amedra Pharmaceuticals with Albenza® (Albendazole) Tablets, 200 mg of Amedra Pharmaceuticals in normal, healthy, adult, human subjects under **fasted conditions**.
2. **Pilot BE Study No. (b) (4) /13/053:** A randomized, open label, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover, bioequivalence study of Albendazole Chewable Tablets, 200 mg of Amedra Pharmaceuticals with Albenza® (Albendazole) Tablets, 200 mg of Amedra Pharmaceuticals in normal, healthy, adult, human subjects under **fed conditions**.

NOTE: The Pilot BE studies (b) (4) /13/052 and (b) (4) /13/053 were not reviewed. The Division of Biopharmaceutics deemed unnecessary the review of these pilot studies.

3. **Pivotal BE Study No. (b) (4) /13/186:** A randomized, open label, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover, bioequivalence study of Albendazole Chewable Tablets, 200 mg of Amedra Pharmaceuticals with Albenza® (Albendazole) Tablets, 200 mg of Amedra Pharmaceuticals in normal, healthy, adult, human subjects under **fasting conditions**.
4. **Pivotal BE Study No. (b) (4) /13/187:** A randomized, open label, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover, bioequivalence study of Albendazole Chewable Tablets, 200 mg of Amedra Pharmaceuticals with Albenza® (Albendazole) Tablets, 200 mg of Amedra Pharmaceuticals in normal, healthy, adult, human subjects under **fed conditions**.

NOTE: The Pivotal BE studies (b) (4) /13/186 and (b) (4) /13/187 were reviewed by the Division of Biopharmaceutics.

5. **BE Inspection:** On 8/18/2014, DAIP requested the Biopharmaceutical Inspection of BE study (b) (4) /13/187.

3. Quality CMC

- **General Quality Considerations**

Drug Substance: The information for albendazole drug substance is referenced to DMF (b)(4). An LOA to reference the DMF was provided. The drug substance for this NDA is the same as that approved under NDA 20-666 for Albenza® Tablets and the DMF was previously reviewed and deemed adequate by Dr. S. Kim under NDA 20-666 (b)(4). Refer to Dr. Kim's review dated 23-SEP-2014. No additional amendments or annual reports have been added to the DMF since the last review.

The drug substance specifications include tests for appearance, identification, organic impurities, assay, solubility, loss on drying, residue on ignition, related substances, residual solvents, and particle size. 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).

Drug Product: The proposed Albenza® Chewable Tablets, 200 mg, is a round, mottled pink, concave tablet debossed with the product code "ap" above "551" on one side and plain on the other side. The chewable tablets are manufactured, packaged, released, and stability tested at (b)(4). Final release of the drug product is the responsibility of **Amedra Pharmaceutical LLC in Horsham, PA.** The quality of the drug product is controlled by tests for appearance, identification, assay, related substances, content uniformity, dissolution, and residual moisture.

- **Stability:**

For commercial use, Albenza® Chewable Tablets, 200 mg, will be packaged in (b)(4), or (b)(4) blisters with either peel push, or push through foil lidding. There are two carton configurations; either 12 tablets (containing 6 count blister cards) or a 2 tablet wallet pack. The Applicant is requesting 24 months of expiration dating and it is supported by 12 months of stability data for 4 batches of drug product packaged in (b)(4) blister packaging configurations (b)(4) blisters.

No meaningful changes were observed in either packaging configuration for up to 12 months under long term conditions and for up to 6 months under accelerated conditions and the requested expiration dating period of 24 months was granted for the drug product.

From the CMC perspective, the overall conclusions are that the NDA included sufficient and adequate stability information to assure the identity, strength, purity, and quality of the drug product through the requested shelf life. The Biopharmaceutics review covers the studies supporting the acceptability of the method and acceptance criteria for the dissolution test.

- **Facilities Review/Inspection:**

The proposed manufacturing site for the manufacturing of Albendazole® Chewable Tablets is (b) (4). The table below includes the specific details of this manufacturing site.

Facility	Responsibilities
(b) (4)	Manufacturing Packaging Release testing Stability testing

Abbreviations: FEI = (Food and Drug Administration) Facility Establishment Identifier; DUNS = Data Universal Numbering System

The Office of Compliance was requested to inspect the manufacturing site of the drug product at (b) (4). On August 26, 2014, the Office of Compliance provided an acceptable recommendation for the manufacturing site of this drug product.

- **CMC Overall Recommendation:**

The CMC Reviewer, Dr. Caroline Strasinger indicates in her review that the following information provides the basis for her overall recommendation; 1) sufficient information provided in the NDA assuring the quality of the drug substance and the drug product, 2) the Product Quality Microbiology Reviewer recommending approval of the NDA, and 3) the Biopharmaceutics Reviewer indicating that the dissolution method and specifications are acceptable. Dr. Strasinger indicates in her review that NDA 207-844 is recommended for **APPROVAL** from a CMC perspective.

For specific details, refer to the CMC review by Dr. Caroline Strasinger dated March 26, 2015 in PANORAMA.

4. Quality Microbiology

The Quality Microbiologist, Dr. Erika Pfeiler in her review dated Nov 14, 2014, states that the Applicant provided a suitable rationale for the exclusion of the microbial limits testing for product release and the Applicant’s proposal to waive the microbial limits testing for product release is acceptable.

Dr. Pfeiler concluded in her review that from a Product Quality Microbiology standpoint **APPROVAL** is recommended for this application.

5. Nonclinical Pharmacology/Toxicology

No new pharmacology/ toxicology data were submitted to this NDA. The labeling information for the relevant pharmacology/toxicology sections is identical to previously approved label. The excipient profile is within levels previously approved for compounds administered by the oral route.

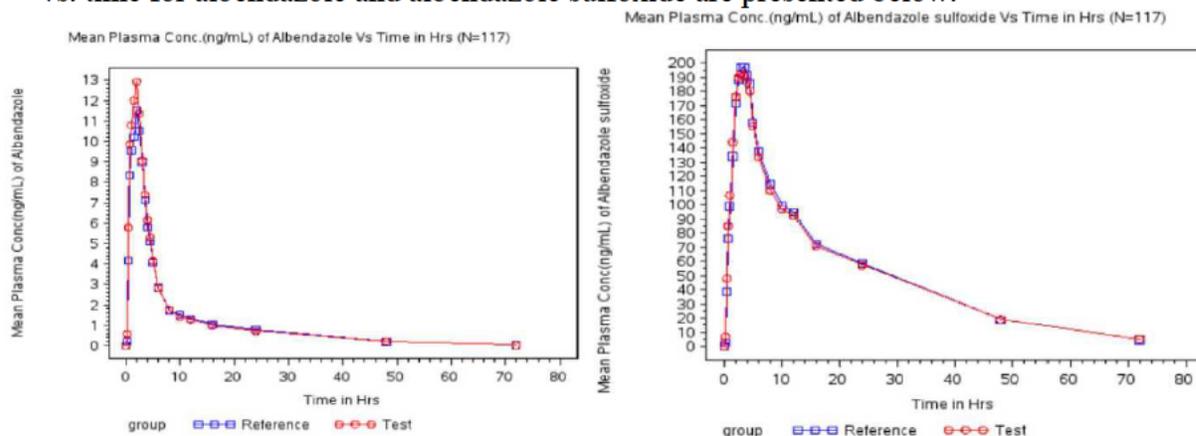
During the Mid-Cycle meeting, the nonclinical pharmacology/toxicology Reviewer, Dr. Wendelyn Schmidt mentioned that there are no pharmacology/toxicology issues with this compound and **APPROVAL** is recommended. It is noted that a final review for the nonclinical pharmacology/toxicology discipline was NOT filed in DARRTS.

6. Biopharmaceutics

The Biopharmaceutics information was reviewed by Dr. Salaheldin Hamed. The primary basis supporting the approval of this new drug application comes from the evaluation of; 1) pivotal bioequivalence study (b)(4)/13/186 conducted under fasted conditions, 2) pivotal bioequivalence study (b)(4)/13/187 conducted under fed conditions, and 3) the proposed method and acceptance criterion for the dissolution test.

• Bioequivalence

- 1) **Pivotal BE Study** (b)(4)/13/186 was an open label, randomized, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover study in healthy male and female subjects under **fasted conditions**. The test product is Albenza® Chewable Tablets, 200 mg (2 tablets for a total dose of 400 mg), Lot# B130391. The reference product is 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 mean plasma concentrations vs. time for albendazole and albendazole sulfoxide are presented below.



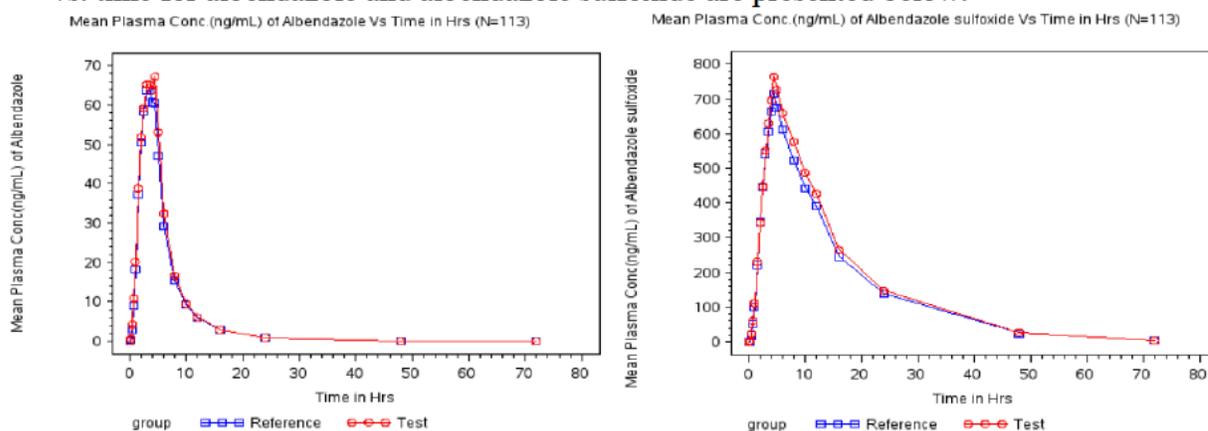
The table below summarizes the statistical results of the pivotal BE fasted study. The geometric mean ratio and the 90% confidence interval for the pharmacokinetic metrics, AUC_0 .

t_{72} , AUC_{inf} , and C_{max} for albendazole and its metabolite, albendazole sulfoxide, are within the 80%-125% acceptable bioequivalence range.

ALB/13/186*	AUC_{0-72}	AUC_{inf}	C_{max}
Albendazole	99 (90-108)	99 (91-111)	105(95-107)
Albendazole Sulfoxide	97 (92-102)	100 (95-04)	103 (98-109)

*T/R ratio with upper and lower values of the 90% Confidence intervals in parenthesis.

- 2) **Pivotal BE Study** ^{(b) (4)}/13/187 was an open label, randomized, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover study in healthy male and female subjects under **fed conditions**. The test product is Albenza® Chewable Tablets, 200 mg (2 tablets for a total dose of 400 mg), Lot# B130391. The reference product is 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 mean plasma concentrations vs. time for albendazole and albendazole sulfoxide are presented below.



The next table summarizes the statistical results of the pivotal BE fed study. The geometric mean ratio and the 90%CI for AUC_{0-72} , AUC_{inf} , and C_{max} for albendazole and the metabolite, albendazole sulfoxide are within the acceptable 80%-125% bioequivalence range.

ALB/13/187*	AUC_{0-72}	AUC_{inf}	C_{max}
Albendazole	102 (91-115)	102 (91-115)	95(84-106)
Albendazole Sulfoxide	110 (103-117)	109 (103-116)	103 (98-109)

- **BE Inspection:**

On 8/18/2014, DAIP requested the Biopharmaceutical Inspection of BE study ^{(b) (4)}/13/187. The inspection report from the Office of Scientific Integrity and Surveillance (OSIS) recommends that the data from this BE study be accepted. For details, refer to the OSIS report dated 4/22/2015 in DARRTS.

- **Dissolution**

- 3) The following dissolution method and acceptance criterion were found acceptable for Quality Control (QC) regulatory purposes for batch release and stability testing.

Dissolution Method and Acceptance Criterion for Albenza® Chewable Tablets

Apparatus	USP II (Paddle)
Medium	0.1 N HCl (900 mL at 37°C)
Rotation Speed	50 rpm
Acceptance Criterion	Q = ^(b) ₍₄₎ % at 30 min

The overall results from BE studies **ALB/13/186** and **ALB/13/187** demonstrated acceptable bioequivalence between the proposed Albenza® Chewable Tablets and the approved Albenza® Tablets, under fed and fasted conditions. The report from OSIS confirms the reliability of the study data and recommends that these data be accepted (OSIS report filed in DARRTS on 4/22/2015).

The Biopharmaceutics review recommends the **APPROVAL** of NDA 207-844 for Albenza® Chewable Tablets. For specific details, refer to the Biopharmaceutics review by Dr. Salaheldin Hamed dated 4/23/2015 in PANORAMA.

7. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Dr. Dakshina Chilukuri, states in his review that the Applicant did not submit any new clinical pharmacology information and therefore there are no additional clinical pharmacology comments on this NDA.

The Clinical Pharmacology review recommends **APPROVAL** of this NDA, pending agreement on the labeling recommended revisions. Refer to the Clinical Pharmacology review by Dr. Dakshina Chilukuri dated 4/21/2015 in DARRTS.

8. Clinical

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug product, Albenza® (albendazole) 200 mg Tablets. However, the clinical review included the evaluation of the pooled safety profile for the four pharmacokinetic pilot and pivotal studies ^(b)₍₄₎/13/052, ^(b)₍₄₎/13/053, ^(b)₍₄₎/13/186, and ^(b)₍₄₎/13/187 conducted to demonstrate bioequivalence of the proposed Albenza® Chewable Tablets, 200 mg to the listed drug product, Albenza® Tablets, 200 mg. No deaths or serious adverse events were reported in these pharmacokinetic studies. 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.

The clinical review concludes that no major unexpected safety signals were noted in the BE studies. The safety update performed by the Applicant was thorough and included the review

of internal, published scientific literature, and FAERS and identified 6 previously unlabeled adverse reactions to be added to the package insert. For full details on the safety assessment, refer to the Clinical review by the Medical Officer, Kimberly C. Martin, D.O., MPH, dated 2/20/2014 in DARRTS.

The clinical review mentions that based on the demonstration of bioequivalence to the currently approved 200 mg tablets, the proposed Albenza® Chewable Tablets is recommended for **APPROVAL** for the same indications as the Listed Drug Product, pending finalization of the BE Inspection report. It is noted that by the date of this CDTL review, the BE Inspection report was already finalized and acceptance of the BE data was recommended.

9. Clinical Microbiology

No new microbiology studies were submitted in the NDA and the Applicant is relying on previous findings of efficacy and safety. This NDA is cross-referenced with NDA20-666. The Microbiology information was submitted under NDA 20666 Vol.1.103– 1.106 on Dec 8, 1995.

The Clinical Microbiology Reviewer, Dr. Lynette Y. Berkeley recommends **APPROVAL** of this NDA. For full details refer to the Clinical Microbiology reviews by Dr. Berkeley dated 10/21/2014 (Label Review) and 12/1/2014 (Final Review) in DARRTS.

10. Clinical Statistical

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on previous findings of the efficacy and safety for the listed drug.

The Biostatistics review dated 6/24/2014, by Dr. Mushfiqur Rashid, Statistical Reviewer reports that this submission did not require statistical evaluation because there were no clinical studies provided in the submission.

11. Safety

There were no clinical studies conducted for the purpose of evaluating the efficacy and safety of the proposed product. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug product. However, the safety of the clinical pharmacokinetic bioequivalence studies ALB/13/186 and ALB/13/187 was evaluated in the clinical review. No deaths or serious adverse events were reported in these studies.

12. Advisory Committee Meeting

The current NDA submission did not go to an Advisory Committee Meeting.

13. Pediatrics

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

14. Other Relevant Regulatory Issues

There are no other additional relevant regulatory issues with this application.

15. Labeling

- **Proprietary Name:** The Applicant's proposed proprietary name Albenza® (albendazole) Chewable Tablet has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found acceptable from both promotional and safety perspectives. For details refer to the DMEPA review by Dr. Danielle Neupauer dated 10/7//2014.
- **Label and Labeling:** The "Label and Labeling Review" from DMEPA dated 11/17/2014 evaluated the Product Information/Prescribing Information, FDA Adverse Event Reporting System (FAERS), Previous DMEPA Reviews, ISMP Newsletters, and Proposed Labels and Labeling. The review concludes that the chewable tablet can be safely introduced to the market and that the proposed packaging size is acceptable. However, the review also concludes that the submitted labels and labeling for Albenza® Tablets 200 mg [REDACTED] (b) (4) and Albenza® Chewable Tablets 200 mg may be improved to promote the safe use of the product and recommends several revisions. For specific/full details refer to the DMEPA review by Dr. Danielle Neupauer and Dr. Tingting Gao dated 10/17/2014.

DAIP also consulted the Office of Prescription Drug Promotion (OPDP) for the review of Albenza Chewable Tablet's draft package insert (PI) and proposed "Wallet card" to determine if the product is acceptable from a medication error perspective. OPDP had no comments on the proposed wallet card; however, OPDP provided several comments for the draft PI. For details, refer to Review Memo by Dr. Puja Shah dated 2/24/2015 in DARRTS.

- **Packaging's Revised Labels:** DMEPA was also consulted for the review of the revised blister label, carton label, and wallet label of Albenza® Chewable Tablets. The review from DMEPA by Dr. Tingting Gao was completed on 11/21/2014 and concludes that the revised blister, carton, and wallet card labels are acceptable from a medication error perspective.
- **Overall Labeling Revisions:** Several revisions were recommended for the proposed labeling by CMC, Biopharmaceutics, Clinical Pharmacology, Clinical, Clinical Microbiology, DMEPA, and OPDP. For the specific recommendations refer to the individual reviews from these disciplines. It is noted that the revisions recommended

by the different disciplines were discussed during the several labeling meetings and the agreed on revisions were incorporated in the labeling of the drug product as appropriate.

- **Conclusion:** A final agreement with the Applicant should be reached on the recommended labeling changes before a regulatory action is taken for this NDA.

16. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** **APPROVAL** with labeling changes is recommended for NDA 207844 for Albenza® (albendazole) Chewable Tablets, 200 mg.
- **Risk Benefit Assessment:** Albendazole is a broad-spectrum anthelmintic effective for the approved indications. The product's labeling adequately informs providers on risks and benefits associated with albendazole use. This application for Albenza® Chewable Tablets relies on FDA's previous findings of safety and effectiveness for the reference drug, Albenza (albendazole) Tablets, 200 mg. No additional safety concerns are expected to be associated with the proposed 200 mg tablets.
- **Recommendation for Postmarketing Risk Evaluation and Management Strategies:** Based on the information available in the current submission and the understanding of albendazole approved therapy, there are no specific recommendations for post-market risk evaluation and mitigation strategies.
- **Recommended Comments to Applicant:** No comments need to be conveyed to the Applicant in the regulatory action letter. However, it is noted that the Applicant has been asked to revise the product's labeling as recommended by the Division of Anti-Infective Products.

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/s/

ANGELICA DORANTES
04/23/2015