

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207844Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Division of Biopharmaceutics/Office of New Drug Products</b>			
<b>Application No.:</b>	NDA 207-844 (000)	<b>Biopharmaceutics Reviewer:</b> Salaheldin S. Hamed, Ph.D.	
<b>Division:</b>	DIAP		
<b>Applicant:</b>	Amedra Pharmaceuticals	<b>Secondary Reviewer:</b> Okpo Eradiri, Ph.D.	
<b>Trade Name:</b>	Albenza® Chewable Tablets	<b>Acting Branch Chief:</b> Angelica Dorantes, Ph.D.	
<b>Generic Name:</b>	Albendazole	<b>Acting Division Director:</b> Paul Seo, Ph.D.	
<b>Indication:</b>	Broad spectrum anthelmintic		
<b>Formulation/strength</b>	Chewable Tablet/200 mg	<b>Date Assigned:</b>	
<b>Route of Administration</b>	Oral	<b>Date of Review:</b>	19-NOV-2014
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<b>Submission Dates</b> Jun 19, 2014 (Original NDA)		<b>Date of informal/Formal Consult</b>	<b>PDUFA DATE</b>
			April 19, 2015
<b>Type of Submission:</b>	505(b)(1)		
<b>Key review points</b>	<ol style="list-style-type: none"> <li>1. Dissolution method and acceptance criteria</li> <li>2. Pivotal bioequivalence (fed and fasted) studies</li> </ol>		
<b>EXECUTIVE SUMMARY</b>			
<p><b>Submission:</b> NDA 207844 for ALBENZA® (albendazole) Chewable Tablets was submitted under section 505(b)(1) of the Food Drug &amp; Cosmetics Act. The Applicant is also the holder of the listed reference drug product, ALBENZA® (albendazole) Tablets, approved under NDA 206666 on June 11, 1996.</p> <p>ALBENZA® is a broad spectrum anthelmintic, indicated for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, <i>Taenia solium</i>, and for the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by larval form of the dog tapeworm, <i>Echinococcus granulosus</i>.</p>			

This NDA provides for an alternative formulation to the approved ALBENZA® 200 mg, white to off-white, circular, biconvex, bevel-edged film coated tablets, which presents a potential choking hazard, particularly in young children. The applicant developed the chewable tablet formulation presented in this NDA, to provide a more desirable, palatable option for patients who have difficulty swallowing tablets.

**Review:** The Biopharmaceutics review is focused on the evaluation of the in vivo pivotal bioequivalence studies and the in vitro dissolution information supporting the approval of this NDA submission.

**IMPORTANT BIOPHARMACEUTICS FINDINGS**

**Bioequivalence Studies**

The results from the pivotal bioequivalence studies (b)(4)/13/186 and (b)(4)/13/187 conducted under fasted and fed conditions, respectively, demonstrated the bioequivalence of the test and listed drug products. As such, both pivotal BE studies are ACCEPTABLE.

**Dissolution**

The following dissolution method and acceptance criterion are ACCEPTABLE for batch release and stability testing.

- Dissolution Method: USP Apparatus II, 50 rpm, 900 mL 0.1 N HCl at 37°C
- Acceptance Criterion: Q = (b)(4)% at 30 min

**RECOMMENDATION**

The Division of Biopharmaceutics had reviewed NDA 207844 for ALBENZA® Chewable Tablets, 200 mg and found the biopharmaceutics in vivo and in vitro data/information adequate. From a Biopharmaceutics perspective, NDA 207844 for ALBENZA® Chewable Tablets is **RECOMMENDED FOR APPROVAL**.

Salaheldin S. Hamed

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Salaheldin S. Hamed, Ph.D.  
Biopharmaceutics Reviewer

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Okpo Eradiri, Ph.D.  
BP Secondary Reviewer

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Angelica Dorantes, Ph.D.  
BP Acting Branch Chief

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**QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION****GENERAL ATTRIBUTES**

1. *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

***Drug Substance***

Albendazole (C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S) is a white to faintly yellowish powder, which is a derivative of benzimidazole carbamate with a molecular mass of 265.3. Albendazole is freely soluble in anhydrous formic acid, very slightly soluble in ether and methylene chloride, and practically insoluble in alcohol or water.

***Drug Product***

The intended drug product is chewable tablets, 200 mg. The tablets are round, mottled pink, concave, and debossed with the product code “ap” above “551” on one side and plain on the other side. The manufacturing process involves (b) (4)  
(b) (4) The components and composition of Albendazole Chewable Tablets, 200 mg are summarized in Table 1.

The Applicant asserts that the excipients used in the proposed drug product were chosen to yield dissolution profile similarity and bioequivalence to the approved drug product, ALBENZA® (NDA 20666). The formulation of the proposed drug product contains excipients commonly used for appearance and palatability, in addition to the (b) (4) tablet excipients of the approved drug product (ALBENZA®), to increase the (b) (4)  
(b) (4)

**Table 1. Components and Composition of Albendazole Chewable Tablets, 200 mg.**

Ingredient	Quality Standard	Function	Quantity per Tablet (mg)
(b) (4)			
Albendazole	3.2.S.4.1	Active ingredient	200.0
Microcrystalline Cellulose (b) (4)	NF	(b) (4)	(b) (4)
Sodium Starch Glycolate (b) (4)	NF		
Lactose Monohydrate (b) (4)	NF		
Povidone (b) (4)	USP		
Sodium Lauryl Sulfate (b) (4)	NF		
(b) (4)	USP		
(b) (4)			(b) (4)
Sodium Starch Glycolate (b) (4)	NF	(b) (4)	(b) (4)
Colloidal Silicon Dioxide (b) (4)	NF	(b) (4)	(b) (4)
Sucralose (b) (4)	NF	(b) (4)	(b) (4)
N-C Wild Berry Type Flavor (b) (4)	3.2.P.4.1 – Wild Berry Flavor	Flavoring agent	14.0
D&C Red #30 Helendon Pink Aluminum Lake (b) (4)			(b) (4)
Magnesium Stearate (b) (4)	NF		(b) (4)
Total Theoretical Weight:			(b) (4)
(b) (4)			

Abbreviations: DMF = Drug Master File, NF = National Formulary, USP = United States Pharmacopeia.

**GENERAL BIOPHARMACEUTICS (IN VITRO)**  
**DISSOLUTION INFORMATION**

*3. What is the proposed dissolution method?*



(b) (4)



(b) (4)

Upon the Agency's request (IR issued on October 16, 2014), the Applicant revised the dissolution rotation speed to 50 rpm and the acceptance criterion to  $Q = \frac{(b)(4)}{(4)}\%$  at 30 minutes. (b) (4)

**4. What data are provided to support the adequacy of the proposed dissolution method (e.g., medium, apparatus selection, etc.)?**

The Applicant did not provide a dissolution method development report. To ensure similar in vivo performance between the approved product and the proposed product, the Applicant utilized the dissolution methodology approved for the listed product ALBENZA® (NDA 20666) to select excipients and manufacturing parameters (e.g., (b) (4) that would result in a similar dissolution profile.

**5. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?**

The dissolution assay method was validated with respect to system suitability, specificity, linearity, accuracy by recovery, repeatability and intermediate precision, filter use, and stability. The validation results are summarized in the following table:

Study	Acceptance Criteria	Results						
System Suitability	All system suitability criteria must pass the requirements stated in the test procedure.	All system suitability requirements were met.						
Specificity	Interference at the retention time of albendazole is NMT <sup>(b)</sup> <sub>(4)</sub> %.	<table border="1"> <thead> <tr> <th>Solution</th> <th>Percent Interference</th> </tr> </thead> <tbody> <tr> <td>Dissolution media</td> <td><sup>(b)</sup><sub>(4)</sub></td> </tr> <tr> <td>Placebo preparation</td> <td>No interference detected</td> </tr> </tbody> </table>	Solution	Percent Interference	Dissolution media	<sup>(b)</sup> <sub>(4)</sub>	Placebo preparation	No interference detected
Solution	Percent Interference							
Dissolution media	<sup>(b)</sup> <sub>(4)</sub>							
Placebo preparation	No interference detected							
Linearity	Correlation coefficient (R) must be $\geq 0.995$ . Percent y-intercept must be within $\pm 3.0\%$ of the 100% response	<table border="1"> <tbody> <tr> <td>Range</td> <td><sup>(b)</sup><sub>(4)</sub></td> </tr> <tr> <td>Correlation Coefficient</td> <td><sup>(b)</sup><sub>(4)</sub></td> </tr> <tr> <td>% y-intercept</td> <td><sup>(b)</sup><sub>(4)</sub></td> </tr> </tbody> </table>	Range	<sup>(b)</sup> <sub>(4)</sub>	Correlation Coefficient	<sup>(b)</sup> <sub>(4)</sub>	% y-intercept	<sup>(b)</sup> <sub>(4)</sub>
Range	<sup>(b)</sup> <sub>(4)</sub>							
Correlation Coefficient	<sup>(b)</sup> <sub>(4)</sub>							
% y-intercept	<sup>(b)</sup> <sub>(4)</sub>							
Method Repeatability	<p>The dissolution results must meet specification of NLT <sup>(b)</sup><sub>(4)</sub>% (Q) of the labeled amount dissolved in 30 minutes.</p> <p>The % RSD for the dissolution results for the six tablets at 30 minutes must be NMT <sup>(b)</sup><sub>(4)</sub></p>	<table border="1"> <thead> <tr> <th>% Dissolved at 30 minutes</th> </tr> </thead> <tbody> <tr> <td><sup>(b)</sup><sub>(4)</sub></td> </tr> </tbody> </table>	% Dissolved at 30 minutes	<sup>(b)</sup> <sub>(4)</sub>				
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Filter Evaluation – <sup>(b)</sup> <sub>(4)</sub>	<sup>(b)</sup> <sub>(4)</sub>							
Stability of Standard Solutions	The response factor for albendazole in the aged solution must be 97.0-103.0% of the response factor in the fresh solution.	The standard solution was found to be stable for 5 days at ambient laboratory conditions.						
Stability of Standard Solutions	The percent of initial for the aged sample solutions should be within 97.0 – 103.0% for the first and last time point.	The sample solutions were found to be stable for 4 days at ambient laboratory conditions						

**6. What data are available to support the discriminating power of the method?**

The Applicant did not investigate the discriminating power of the dissolution method systematically. However, the dissolution method was able to discriminate the scale-up batch (RD13013) with <sup>(b)</sup><sub>(4)</sub>. In addition, the dissolution

method was able to discriminate the batch manufactured (b) (4) (see Figure 2)



**7. Is the proposed dissolution method biorelevant? What data are available to support this claim?**

No, the proposed dissolution method is NOT biorelevant.

**8. Is the proposed method acceptable? If not, what are the deficiencies?**

The originally proposed method was not accepted. Upon the Agency's request (IR issued on October 16, 2014), the Applicant revised the dissolution rotation speed from (b) (4) rpm to 50 rpm.

## ACCEPTANCE CRITERION

**9. What is the proposed dissolution acceptance criterion for this product?**

Q = (b) (4)

**10. What data are available to support the criteria?**

The Applicant provided individual vessel dissolution data for 6 unit doses of the laboratory scale batch (B130267), the failed scale-up batch (RD13013), and the 3 registration batches (B130402, B130403, and B130404) at 10, 15, 20, 30, 45, and 60 minutes.

**11. Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?**

The Applicant provided dissolution data for 3 registration batches (B130402, B130403, and B130404). Batch B130402 was used for clinical studies.

**12. Are mean (n = 12) dissolution profile data used for the setting of the acceptance criteria?**

No. The Applicant provided mean (b) (4) data for each of the batches listed above.

**13. Is the acceptance criterion acceptable? If not, what is the recommended criterion?**

The proposed criterion of (b) (4) was not supported by the overall dissolution data and was NOT accepted. Upon the Agency's request (IR issued on October 16, 2014), the Applicant revised the dissolution acceptance criterion to  $Q = (b) (4)\%$ .

**Reviewer's Overall Assessment of Dissolution: ACCEPTABLE**

*The following dissolution method and acceptance criterion have been agreed upon with the Applicant and are acceptable for batch release and on stability testing.*

- Dissolution Method: USP Apparatus II, 50 rpm, 900 mL 0.1 N HCl at 37°C
- Acceptance Criterion:  $Q = (b) (4)\%$  at 30 min

**Reviewer's Notes:**

*The dissolution methodology of the approved product, ALBENZA® Tablets, was used to select components of the formulation that would result in a similar dissolution profile for the proposed Chewable Tablets in vitro, which would be expected to result in similar performance in vivo. The dissolution methodology was able to discriminate the scale-up batch with faulty LoD sampling method (b) (4) and pilot commercial batches with (b) (4). It is worth noting, however, that the Applicant did not systematically investigate the discriminating ability of the dissolution methodology on relevant manufacturing parameters such as (b) (4).*

*The drug substance is not readily soluble and, based on the reported data, the mean dissolution for the reported batches (b) (4). In addition, the mean dissolution value exhibits (b) (4) (see Figure 1, top panel). As such, the 30-minute time point is ADEQUATE. The dissolution conditions (50 rpm (b) (4)).*

*The stability data are provided for drug product packaged in (b) (4) foil laminate blisters through 6 months of storage at long-term conditions (25°C/60% RH) and accelerated conditions (40°C/75% RH). The dissolution profile for (b) (4) dosage units at 15, 30, 45, and 60 minutes was provided. The mean dissolution value at 30 minutes was higher than (b) (4)%.*

## DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING

### *14. What are the highlights of the drug product formulation development?*

The manufacturing process involves

(b) (4)

(b) (4)

### *15. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?*

The proposed product is available in 1 strength, 200 mg, which was evaluated in 4 Bioequivalence studies: 2 pilot studies (1 fed and 1 fasted) and 2 pivotal studies (1 fed and 1 fasted).

## DISSOLUTION APPLICATIONS

### *A. FORMULATION CHANGES*

#### *16. Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?*

The to-be-marketed formulation is the same as the formulation used in the pilot and pivotal bioequivalence studies.

#### *17. Is the finished tablet scored? Do the dissolution data comparing the split versus whole tablet support tablet splitting?*

No. The finished product is not scored.

### *B. BIOWAIVER REQUESTS*

#### *18. Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?*

There is no biowaiver request in this application.

## GENERAL BIOPHARMACEUTICS (IN VIVO)

### *19. What are the biopharmaceutics studies used to support the proposed to-be-marketed drug product?*

Four biopharmaceutics studies were completed to support the approval of the proposed to-be-marketed product: 2 pilot studies (fasted, (b) (4)/13/052, and fed, (b) (4)/13/053) and 2 pivotal studies (fasted, (b) (4)/13/186, and fed, (b) (4)/13/187). The biopharmaceutics review is being focus only on the evaluation of the two pivotal studies. Since the pilot BE studies were not needed to support approval, the review of the pilot studies was deemed unnecessary.

## BIOEQUIVALENCE STUDIES

### *20. What are the design features of the bioequivalence studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided*

The design features and results of the two pivotal bioequivalence studies are summarized below:

- Study (b) (4)/13/187, fed bioequivalence study
- Study (b) (4)/13/186, fasted bioequivalence study

<b>Study (b) (4)/13/187 (FED BE)</b>	
<b>STUDY DESIGN</b>	An open label, randomized, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover study in healthy male and female subjects. 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.
<b>METHODOLOGY</b>	The order of administration was according to a randomization schedule, with a 7-day washout period between each treatment period. Blood samples were collected at pre-dose (0.00 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. Physical examinations, clinical laboratory assessments, vital sign measurements, and 12-lead ECG were assessed during the conduct of the study.  Statistical analysis was performed on the pharmacokinetic data to compare the relative bioavailability of test formulation to the reference formulation using SAS. Bioequivalence was determined by a statistical comparison of the AUC <sub>0-72</sub> , AUC <sub>inf</sub> , and C <sub>max</sub> for the test and reference products. The secondary parameters T <sub>max</sub> ,

	$K_{el}$ , and half-life were also analyzed.																																																																																																
<b>SUBJECTS/ DEMOGRAPHICS</b>	<p>According to the Applicant's sample size estimation for crossover study, assuming T/R = 0.95, within-subject CV% of 58%, power = 80%, significance level = 0.05, BE limits = 0.8-1.25, a sample size of 126 was considered sufficient to demonstrate bioequivalence.</p> <p>A total of 126 subjects were enrolled, and data from 113 subjects were considered for bioequivalence. Three subjects (21, 23, and 83) were discontinued due to emesis, two subjects (84 and 101) were discontinued for protocol non-compliance, and 8 subjects (45, 54, 55, 69, 70, 76, 108, and 126) dropped out of the study.</p> <table border="1"> <thead> <tr> <th></th> <th>Age (year)</th> <th>Height (cm)</th> <th>Weight (kg)</th> <th>BMI (kg/m<sup>2</sup>)</th> </tr> </thead> <tbody> <tr> <td>Number of observation</td> <td></td> <td></td> <td>113</td> <td></td> </tr> <tr> <td>Mean</td> <td>30.21</td> <td>165.70</td> <td>62.41</td> <td>22.74</td> </tr> <tr> <td>Minimum</td> <td>18</td> <td>140</td> <td>50</td> <td>18.56</td> </tr> <tr> <td>Maximum</td> <td>45</td> <td>184</td> <td>84</td> <td>29.76</td> </tr> <tr> <td>SD</td> <td>06.84</td> <td>07.13</td> <td>08.99</td> <td>05.04</td> </tr> <tr> <td>Median</td> <td>30.00</td> <td>166.00</td> <td>63.00</td> <td>22.32</td> </tr> </tbody> </table>		Age (year)	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )	Number of observation			113		Mean	30.21	165.70	62.41	22.74	Minimum	18	140	50	18.56	Maximum	45	184	84	29.76	SD	06.84	07.13	08.99	05.04	Median	30.00	166.00	63.00	22.32																																																													
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<b>SUMMARY OF RESULTS</b>	<p>There were 41 blood sampling protocol deviations during the 3 periods of the study at the 48- and 72-hour time point due to subject not reporting to the study site. The impact of missing samples was considered during pharmacokinetic and statistical analysis. The statistical analysis for albendazole are summarized in the following table:</p> <table border="1"> <thead> <tr> <th colspan="4">Statistical Analysis Data for ln-transformed parameters</th> </tr> <tr> <th></th> <th><math>C_{max}</math></th> <th><math>AUC_{0-12}</math></th> <th><math>AUC_{0-24}</math></th> </tr> </thead> <tbody> <tr> <td colspan="4">ANOVA p-value</td> </tr> <tr> <td>Sequence</td> <td>0.0147</td> <td>0.7538</td> <td>0.8713</td> </tr> <tr> <td>Acceptance criteria for Ratio</td> <td>0.80-1.25</td> <td>0.80-1.25</td> <td>0.80-1.25</td> </tr> <tr> <td>Ratio of Geometric Least Square Means (A/B)</td> <td>1.0528</td> <td>0.9866</td> <td>1.0221</td> </tr> <tr> <td>Acceptance Criteria for 95% Confidence Bound</td> <td>±0.0000</td> <td>±0.0000</td> <td>±0.0000</td> </tr> <tr> <td>95% Confidence Upper Bound</td> <td>-0.1933</td> <td>-0.1860</td> <td>-0.1689</td> </tr> <tr> <td>Reference Scaled Average Bioequivalence Acceptance</td> <td>Bioequivalent</td> <td>Bioequivalent</td> <td>Bioequivalent</td> </tr> </tbody> </table> <p>The Applicant did not provide statistical analysis results for the metabolite albendazole sulfoxide. However, the PK parameters for the test (A) and reference (B) formulations are summarized in the following table:</p> <table border="1"> <thead> <tr> <th colspan="5">Descriptive Statistics for Untransformed parameters</th> </tr> <tr> <th>Measures</th> <th><math>C_{max}</math> (ng/mL)</th> <th><math>AUC_{0-12}</math> (ng*hr/mL)</th> <th><math>AUC_{0-24}</math> (ng*hr/mL)</th> <th><math>T_{max}</math> (hr)</th> </tr> </thead> <tbody> <tr> <td colspan="5"><b>Test Product- A</b></td> </tr> <tr> <td>N</td> <td>113</td> <td>113</td> <td>113</td> <td>113</td> </tr> <tr> <td>Mean</td> <td>808.525</td> <td>11095.485</td> <td>11543.786</td> <td>4.508*</td> </tr> <tr> <td>SD</td> <td>409.345</td> <td>7150.141</td> <td>7176.129</td> <td>1.537</td> </tr> <tr> <td>CV (%)</td> <td>50.628</td> <td>64.442</td> <td>62.164</td> <td>29.745</td> </tr> <tr> <td colspan="5"><b>Reference Product- B</b></td> </tr> <tr> <td>N</td> <td>230</td> <td>230</td> <td>230</td> <td>230</td> </tr> <tr> <td>Mean</td> <td>785.267</td> <td>10402.503</td> <td>10856.587</td> <td>4.500*</td> </tr> <tr> <td>SD</td> <td>381.877</td> <td>7514.229</td> <td>7554.492</td> <td>1.483</td> </tr> <tr> <td>CV (%)</td> <td>48.630</td> <td>72.235</td> <td>69.584</td> <td>34.404</td> </tr> </tbody> </table> <p>*Median value has been represented instead of Mean</p> <p>The mean PK profiles of the reference and test formulations are presented in the following figures:</p>	Statistical Analysis Data for ln-transformed parameters					$C_{max}$	$AUC_{0-12}$	$AUC_{0-24}$	ANOVA p-value				Sequence	0.0147	0.7538	0.8713	Acceptance criteria for Ratio	0.80-1.25	0.80-1.25	0.80-1.25	Ratio of Geometric Least Square Means (A/B)	1.0528	0.9866	1.0221	Acceptance Criteria for 95% Confidence Bound	±0.0000	±0.0000	±0.0000	95% Confidence Upper Bound	-0.1933	-0.1860	-0.1689	Reference Scaled Average Bioequivalence Acceptance	Bioequivalent	Bioequivalent	Bioequivalent	Descriptive Statistics for Untransformed parameters					Measures	$C_{max}$ (ng/mL)	$AUC_{0-12}$ (ng*hr/mL)	$AUC_{0-24}$ (ng*hr/mL)	$T_{max}$ (hr)	<b>Test Product- A</b>					N	113	113	113	113	Mean	808.525	11095.485	11543.786	4.508*	SD	409.345	7150.141	7176.129	1.537	CV (%)	50.628	64.442	62.164	29.745	<b>Reference Product- B</b>					N	230	230	230	230	Mean	785.267	10402.503	10856.587	4.500*	SD	381.877	7514.229	7554.492	1.483	CV (%)	48.630	72.235	69.584	34.404
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	$C_{max}$	$AUC_{0-12}$	$AUC_{0-24}$																																																																																														
ANOVA p-value																																																																																																	
Sequence	0.0147	0.7538	0.8713																																																																																														
Acceptance criteria for Ratio	0.80-1.25	0.80-1.25	0.80-1.25																																																																																														
Ratio of Geometric Least Square Means (A/B)	1.0528	0.9866	1.0221																																																																																														
Acceptance Criteria for 95% Confidence Bound	±0.0000	±0.0000	±0.0000																																																																																														
95% Confidence Upper Bound	-0.1933	-0.1860	-0.1689																																																																																														
Reference Scaled Average Bioequivalence Acceptance	Bioequivalent	Bioequivalent	Bioequivalent																																																																																														
Descriptive Statistics for Untransformed parameters																																																																																																	
Measures	$C_{max}$ (ng/mL)	$AUC_{0-12}$ (ng*hr/mL)	$AUC_{0-24}$ (ng*hr/mL)	$T_{max}$ (hr)																																																																																													
<b>Test Product- A</b>																																																																																																	
N	113	113	113	113																																																																																													
Mean	808.525	11095.485	11543.786	4.508*																																																																																													
SD	409.345	7150.141	7176.129	1.537																																																																																													
CV (%)	50.628	64.442	62.164	29.745																																																																																													
<b>Reference Product- B</b>																																																																																																	
N	230	230	230	230																																																																																													
Mean	785.267	10402.503	10856.587	4.500*																																																																																													
SD	381.877	7514.229	7554.492	1.483																																																																																													
CV (%)	48.630	72.235	69.584	34.404																																																																																													

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	<p>Mean Plasma Conc (ng/ml) of Alendazole Vs Time in Hrs (N=13)</p> <p>Mean Logarithmic Conc (ng/ml) of Alendazole Vs Time in Hrs (N=13)</p> <p>Mean Plasma Conc (ng/ml) of Alendazole sulfoxide Vs Time in Hrs (N=13)</p> <p>Mean Logarithmic Conc (ng/ml) of Alendazole sulfoxide Vs Time in Hrs (N=13)</p>
<p><b>SUMMARY OF SAFETY</b></p>	<p>A total of 3 adverse events (AEs) were reported for 3 subjects (vomiting) during the study. All AEs were mild in severity.</p>

<b>Study <sup>(b) (4)</sup>/13/186 (FASTED BE)</b>																																				
<b>STUDY DESIGN</b>	An open label, randomized, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, crossover study in healthy male and female subjects. 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.																																			
<b>METHODOLOGY</b>	<p>The order of administration was according to a randomization schedule, with a 7-day washout period between each treatment period. Blood samples were collected at pre-dose (0.00 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.</p> <p>Physical examinations, clinical laboratory assessments, vital sign measurements, and 12-lead ECG were assessed during the conduct of the study.</p> <p>Statistical analysis was performed on the pharmacokinetic data to compare the relative bioavailability of test formulation to the reference formulation using SAS. Bioequivalence was determined by a statistical comparison of the <math>AUC_{0-72}</math>, <math>AUC_{mf}</math>, and <math>C_{max}</math> for the test and reference products. The secondary parameters <math>T_{max}</math>, <math>K_{el}</math>, and half-life were also analyzed.</p>																																			
<b>SUBJECTS/ DEMOGRAPHICS</b>	<p>According to the Applicant's sample size estimation for crossover study, assuming <math>T/R = 0.95</math>, within-subject CV% of 58%, power = 80%, significance level = 0.05, BE limits = 0.8-1.25, a sample size of 126 was considered sufficient to demonstrate bioequivalence.</p> <p>A total of 126 subjects were enrolled, and data from 117 subjects were considered for assessing bioequivalence. Three subjects (39, 102, and 116) were discontinued due to protocol non-compliance, one subject (75) was discontinued due to dizziness, one subject (105) was discontinued due to fever, and 4 subjects (42, 58, 101, and 108) dropped out of the study.</p>																																			
<b>BEST AVAILABLE COPY</b>	<table border="1"> <thead> <tr> <th>Number of observation</th> <th>Age (year)</th> <th>Height (cm)</th> <th>Weight (kg)</th> <th>BMI (kg/m<sup>2</sup>)</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td>117</td> </tr> <tr> <td>Mean</td> <td>30.15</td> <td>165.97</td> <td>62.26</td> <td>22.59</td> </tr> <tr> <td>Minimum</td> <td>18</td> <td>150</td> <td>50</td> <td>18.51</td> </tr> <tr> <td>Maximum</td> <td>44</td> <td>180</td> <td>94</td> <td>29.74</td> </tr> <tr> <td>SD</td> <td>06.98</td> <td>06.15</td> <td>09.46</td> <td>03.07</td> </tr> <tr> <td>Median</td> <td>30.00</td> <td>167.00</td> <td>60.00</td> <td>21.93</td> </tr> </tbody> </table>	Number of observation	Age (year)	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )					117	Mean	30.15	165.97	62.26	22.59	Minimum	18	150	50	18.51	Maximum	44	180	94	29.74	SD	06.98	06.15	09.46	03.07	Median	30.00	167.00	60.00	21.93
Number of observation	Age (year)	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )																																
				117																																
Mean	30.15	165.97	62.26	22.59																																
Minimum	18	150	50	18.51																																
Maximum	44	180	94	29.74																																
SD	06.98	06.15	09.46	03.07																																
Median	30.00	167.00	60.00	21.93																																
<b>SUMMARY OF RESULTS</b>	There were 27 blood sampling protocol deviations during the 3 periods of the study at the 48- or 72-hour time point due to subjects not reporting to the study site. The impact of missing samples was considered during pharmacokinetic and statistical analysis.																																			

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**Statistical Analysis of Albendazole Parent Drug PK Parameters**

Statistical Analysis Data for ln-transformed parameters

Sequence	C <sub>50%</sub> ANOVA p-value	AUC <sub>0-∞</sub>	AUC <sub>0-8h</sub>
Acceptance criteria for Ratio	0.80-1.25	0.80-1.25	0.80-1.25
Ratio of Geometric Least Square Means (A/B)	0.9353	1.0355	1.0333
Acceptance Criteria for 95% Confidence Bound	±0.0000	±0.0000	±0.0000
95% Confidence Upper Bound	-0.1568	-0.1849	-0.1743
Reference Scaled Average Bioequivalence Acceptance	Bioequivalent	Bioequivalent	Bioequivalent

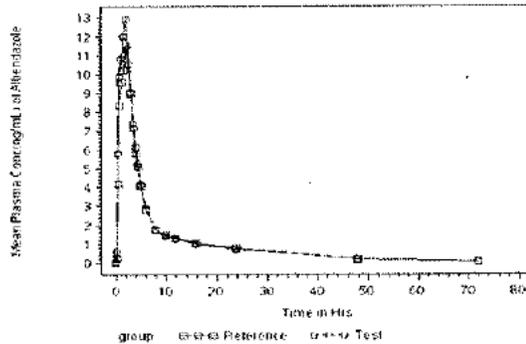
The Applicant did not provide statistical analysis of the metabolite albendazole sulfoxide. However, the PK parameters are summarized in the following table:

Descriptive Statistics for Untransformed parameters

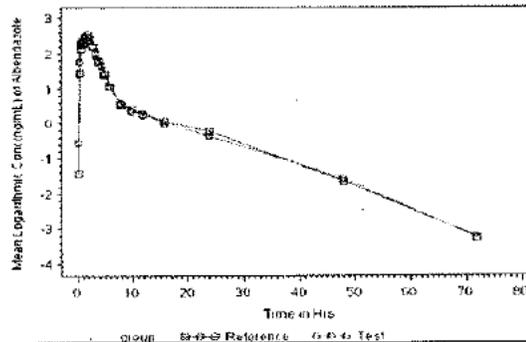
Measures	C <sub>max</sub> (ng/mL)	AUC <sub>0-∞</sub> (ng*hr/mL)	AUC <sub>0-8h</sub> (ng*hr/mL)	T <sub>max</sub> (hr)
<b>Test Product- A</b>				
N	117	117	117	117
Mean	217.679	3472.678	3862.355	2.500*
SD	118.479	1882.477	2025.748	1.037
CV (%)	53.050	54.208	52.397	37.372
<b>Reference Product- B</b>				
N	236	236	236	236
Mean	215.884	3505.738	3802.549	2.500*
SD	117.493	1774.024	1813.268	0.974
CV (%)	54.424	50.603	47.686	34.437

\* Median value has been represented instead of Mean.

Mean Plasma Conc (ng/mL) of Albendazole Vs Time in Hrs (N=117)



Mean Logarithmic Conc (ng/mL) of Albendazole Vs Time in Hrs (N=117)



<p><b>BEST AVAILABLE COPY</b></p>	<p style="text-align: center;">Mean Plasma Conc (ng/mL) of Albendazole sulfoxide Vs Time in Hrs (N=117)</p> <p style="text-align: center;">Mean Logarithmic Conc (ng/mL) of Albendazole sulfoxide Vs Time in Hrs (N=117)</p>
<p><b>SUMMARY OF SAFETY</b></p>	<p>A total of 3 adverse events (AEs) were reported for 3 subjects (vomiting) during the study. All AEs were mild in severity.</p>

**Reviewer's Evaluation: ACCEPTABLE**

Both the fasting and fed studies were executed using acceptable protocols for demonstrating BE (e.g., sample size, dosing schedule, washout period, statistical method). There were no observed deviations in any study that could impact study outcomes and the justifications provided for excluding any subject data from the PK analysis are acceptable (i.e., incomplete data, emesis, etc.). 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, are within the acceptance range of 80%-125%.

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)

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. The reported values are the reviewer's calculated values based on average bioequivalence.

**BIOANALYTICAL METHODS**

***21. How the active moieties and/or metabolites are identified and measured in the plasma in the biopharmaceutics studies?***

In vivo analysis is based on the measured concentrations of Albendazole and Albendazole Sulfoxide in plasma using a validated LC-MS/MS method.

***22. What is the range of standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.)?***

<b>Matrix</b>	<b>Human Plasma</b>
<b>Sample Volume Required</b> <b>Storage Conditions</b> <b>Extraction Procedure</b>	<p>Sample Volume Required: 0.100 mL Storage Conditions: -70°C ± 10°C Extraction Procedure:</p> <p>Thaw all frozen plasma samples (System suitability, blank plasma, zero standard, calibration curve standards and quality control samples) before analysis. Vortex each plasma sample for 10 seconds.</p> <p>Extract plasma samples of Albendazole and Albendazole Sulfoxide by solid phase extraction method as described below:</p> <ol style="list-style-type: none"> <li>1. Place an appropriate number of centrifuge tubes in a rack</li> <li>2. Pipette out 0.100 mL plasma sample into previously labeled tubes.</li> <li>3. Add 0.025 mL of IS1 (0.200 µg/mL of Albendazole d3 and 3.000 µg/mL of Albendazole-d5 sulfoxide) in each tube and vortex it for 10 seconds.</li> <li>4. Add 0.100 mL of 2mM ammonium acetate in water in each tube, vortex it for 30 seconds.</li> <li>5. Centrifuge the samples at 14000 RPM for 5 minutes at 10°C</li> <li>6. Condition and equilibrate SPE cartridge [Phenomenex strata- X (30mg/mL)] by passing 1.000 mL of methanol followed by 1.000 mL of water.</li> <li>7. Load plasma samples on the cartridges.</li> <li>8. Drain out the plasma by applying pressure.</li> <li>9. Wash the cartridges twice with 1.000 mL of 10% (v/v) methanol in water.</li> <li>10. Elute the samples with 2.000 mL of mobile phase.</li> <li>11. Transfer it in autosampler vial for injection.</li> </ol>

<b>Matrix</b>	<b>Human Plasma</b>									
<b>Concentration Range</b>	Albendazole: 1.000 ng/mL to 199.995 ng/mL Albendazole Sulfoxide: 9.000 ng/mL to 1800.000 ng/mL									
<b>Analytical Methodology</b>	Solid phase extraction, LC-MS/MS									
<b>Detection</b>	MRM									
<b>Regression Type</b>	1/x <sup>2</sup>									
<b>Coefficient of Determination</b>	Albendazole: 0.9980 Albendazole Sulfoxide: 0.9980									
<b>Between-Batch Accuracy</b>	Standards QCs	<p>Albendazole: NA Albendazole Sulfoxide: NA</p> <p>Albendazole:</p> <table border="1"> <tr> <td>LLQC: 92.00</td> <td>LQC: 98.25</td> </tr> <tr> <td>MQC: 90.28</td> <td>HQC: 100.29</td> </tr> </table> <p>Albendazole Sulfoxide:</p> <table border="1"> <tr> <td>LLQC: 89.93</td> <td>LQC: 97.31</td> </tr> <tr> <td>MQC: 89.80</td> <td>HQC: 99.60</td> </tr> </table>	LLQC: 92.00	LQC: 98.25	MQC: 90.28	HQC: 100.29	LLQC: 89.93	LQC: 97.31	MQC: 89.80	HQC: 99.60
LLQC: 92.00	LQC: 98.25									
MQC: 90.28	HQC: 100.29									
LLQC: 89.93	LQC: 97.31									
MQC: 89.80	HQC: 99.60									
<b>Between Batch CV</b>	Standards QCs	<p>Albendazole: NA Albendazole Sulfoxide: NA</p> <p>Albendazole:</p> <table border="1"> <tr> <td>LLQC: 4.13</td> <td>LQC: 2.65</td> </tr> <tr> <td>MQC: 1.72</td> <td>HQC: 2.11</td> </tr> </table> <p>Albendazole Sulfoxide:</p> <table border="1"> <tr> <td>LLQC: 5.02</td> <td>LQC: 2.58</td> </tr> <tr> <td>MQC: 1.90</td> <td>HQC: 2.33</td> </tr> </table>	LLQC: 4.13	LQC: 2.65	MQC: 1.72	HQC: 2.11	LLQC: 5.02	LQC: 2.58	MQC: 1.90	HQC: 2.33
LLQC: 4.13	LQC: 2.65									
MQC: 1.72	HQC: 2.11									
LLQC: 5.02	LQC: 2.58									
MQC: 1.90	HQC: 2.33									

Matrix	Human Plasma		
Within-Batch	Accuracy	Albendazole:	
		CS01: 98.40      CS02: 105.60      CS03: 95.63	
		CS04: 97.93      CS05: 100.35      CS06: 105.83	
		CS07: 93.30      CS08: 101.22      CS09: 101.72	
		LLQC: 90.80 to 93.70      LQC: 97.11 to 99.21	
		MQC: 89.53 to 90.82      HQC: 99.76 to 100.91	
		Albendazole Sulfoxide:	
	CS01: 99.77      CS02: 102.16      CS03: 97.28		
	CS04: 97.06      CS05: 102.32      CS06: 104.30		
	CS07: 92.44      CS08: 101.47      CS09: 103.21		
	LLQC: 88.19 to 93.10      LQC: 95.99 to 99.43		
	MQC: 89.06 to 90.20      HQC: 98.77 to 100.19		
	CV	Albendazole:	CS01: 0.61      CS02: 0.76      CS03: 0.97
			CS04: 1.17      CS05: 0.89      CS06: 1.13
CS07: 1.99      CS08: 1.86      CS09: 0.90			
LLQC: 3.28 to 5.29      LQC: 1.73 to 3.66			
MQC: 1.32 to 2.09      HQC: 1.38 to 2.69			
Albendazole Sulfoxide:		CS01: 1.10      CS02: 1.08      CS03: 2.38	
		CS04: 1.17      CS05: 1.35      CS06: 2.08	
		CS07: 1.65      CS08: 0.75      CS09: 1.32	
		LLQC: 3.21 to 5.23      LQC: 0.90 to 3.09	
		MQC: 1.50 to 2.34      HQC: 1.30 to 3.67	
Recovery	Drug Reference	Albendazole: 84.06 Albendazole Sulfoxide: 80.51 Albendazole-d3: 93.29 Albendazole-d5 Sulfoxide: 89.46	
Stability in Human Plasma	Room temp Freeze/thaw Long term	7 hours Five cycles 107 days at -70°C ± 10°C	
Solution Stability	Room temp 4°C	19 hours 6 days at 2-8°C	
Reference Solution Stability	Room temp 4°C	NA NA	

Matrix	Human Plasma	
LLOQ (Accuracy/CV)	Accuracy	Albendazole: 0.61 Albendazole Sulfoxide: 1.10
	CV	Albendazole: 98.40 Albendazole Sulfoxide: 99.77
Processed Stability	4°C	7 hours at room temperature, 50 hours at 5°C
Dilution Integrity (v:v sample-blank)	Concentration diluted up to 1/2 times and 1/4 times	

### 23. What is the QC plan?

QC samples were used to monitor accuracy and precision of the method. QC samples were prepared by spiking blank plasma with spiking solution of known concentrations of Albendazole and Albendazole sulfoxide as shown in the following table

**PREPARATION OF QUALITY CONTROL SAMPLES**

Vol. of blank plasma (mL)	Vol. of spiking solution to be used	Final vol. (mL)	Final conc. (ng/mL)		QC samples
			ALB	ALS	
0.095	0.005 mL of J	0.100	0.200	3.000	LLQC
0.095	0.005 mL of K	0.100	0.560	8.400	LQC
0.095	0.005 mL of L	0.100	6.500	78.000	M1QC
0.095	0.005 mL of M	0.100	16.000	192.000	M2QC
0.095	0.005 mL of N	0.100	40.000	480.000	HQC

For study (b) (4)/13/187, 686 samples were analyzed from random subjects, and a total of 97.32% of samples were found to be within  $\pm 20\%$  of the original assay values. For study (b) (4)/13/186, 695 samples were analyzed from random subjects, and total of 98.70% of samples were found to be within  $\pm 20\%$  of the original assay value.

### 24. Are the Inspection reports of the BE study acceptable?

The Report from the Office of Study Integrity and Surveillance for the audit of the analytical and clinical sites of bioequivalence study (b) (4)/13/187 confirms the reliability of the study data (see Establishment Inspection Report Review, DARRTS 04/22/2015). It is noted that the reliability of the data recommendation for study (b) (4)/13/187, also applies to study (b) (4)/13/186, which was conducted at the same analytical and clinical sites.

### REVIEWER'S OVERALL ASSESSMENT OF BE STUDIES

The pivotal (fed) bioequivalence study, (b) (4)/13/187, and the supportive (fasting) bioequivalence study, (b) (4)/13/186, are **ACCEPTABLE** based on the conduct and PK data statistical analysis.

### **LABELING**

Biopharmaceutics was required to evaluate the labeling section pertaining to PK data and effect food in section 12.3 of the label. The proposed Biopharmaceutics label is as follows:

*In a study conducted in 113 fed and 117 fasted healthy subjects, Albenza chewable tablets were bioequivalent to Albenza tablets following single 400 mg oral doses of albendazole. In this study, the average time to reach the maximal plasma concentrations of albendazole sulfoxide was*

4.5 hours (range 2 to 10 hours) with a fatty meal (fat content 60 grams) and at 3 hours (range 1 to 5 hours) in the fasted state. Following administration of Albenza chewable tablets, average maximal plasma concentrations of albendazole sulfoxide were 804 ng/mL (range 202 to 2244 ng/mL) and 218 ng/mL (range 54 to 592 ng/mL) in the fed and fasted states, respectively. The apparent elimination half-life of albendazole sulfoxide was comparable between Albenza chewable tablets and Albenza tablets when both were given either under fed or fasted conditions.

The PK data from the pivotal fasted and fed BE studies (See Appendix) was used to support labeling.

## INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses to these questions are incorporated in QBR above. There are not outstanding review issues

- 1. We could not locate the dissolution method development report within the NDA; if it was included in the original submission, please provide the CTD location. In the event that this report was omitted, provide data that support the suitability and discriminating ability of the proposed dissolution method for your product. If the proposed method is similar to that for the approved oral tablet in NDA 20666, provide a comparison of the two methods, explaining the rationale for any changes that may have been made for the proposed product.*
- 2. The proposed dissolution acceptance criterion of  $Q = \text{(b) (4)}$  is neither supported by the release data for batches B130402, B130403 and B130404 nor adequately justified. Your current method results in approximately  $\text{(b) (4)}\%$   $\text{(b) (4)}$ .  $\text{(b) (4)}$  Per the guidelines provided above, please investigate the discriminating power of the proposed method and modify the method and/or the proposed acceptance criterion accordingly. Thereafter, update the Specifications Table to reflect the new dissolution acceptance criterion.*
- 3. Confirm the mode of drug administration in the pivotal bioavailability study  $\text{(b) (4)}$ /13/187, i.e., if the test product was chewed or swallowed whole.*

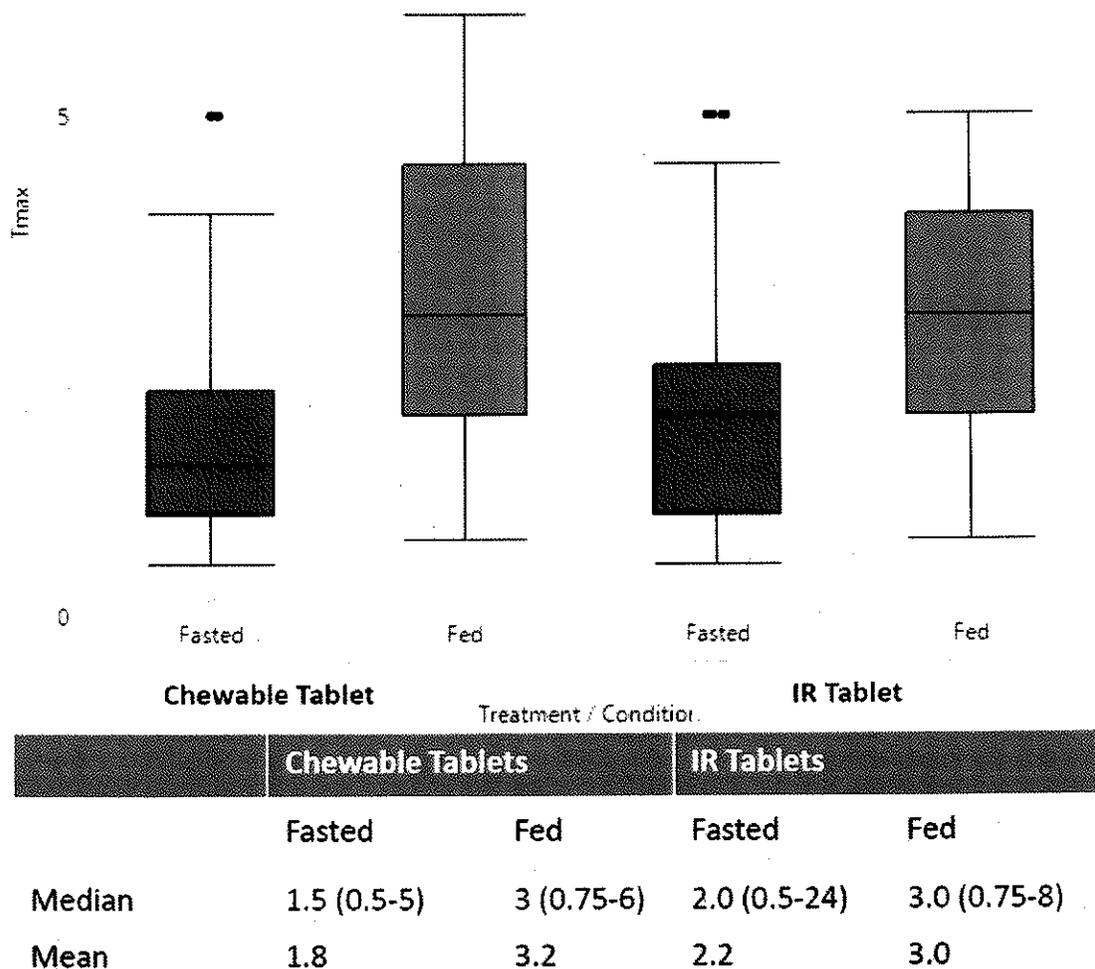
### Sponsor's Response

In the pivotal bioequivalence study  $\text{(b) (4)}$ /13/187, subjects were instructed not to chew or crush the tablet but to swallow it whole with 240 ml of water at ambient temperature (reference  $\text{(b) (4)}$ /13/187 study protocol, Section 5.1).

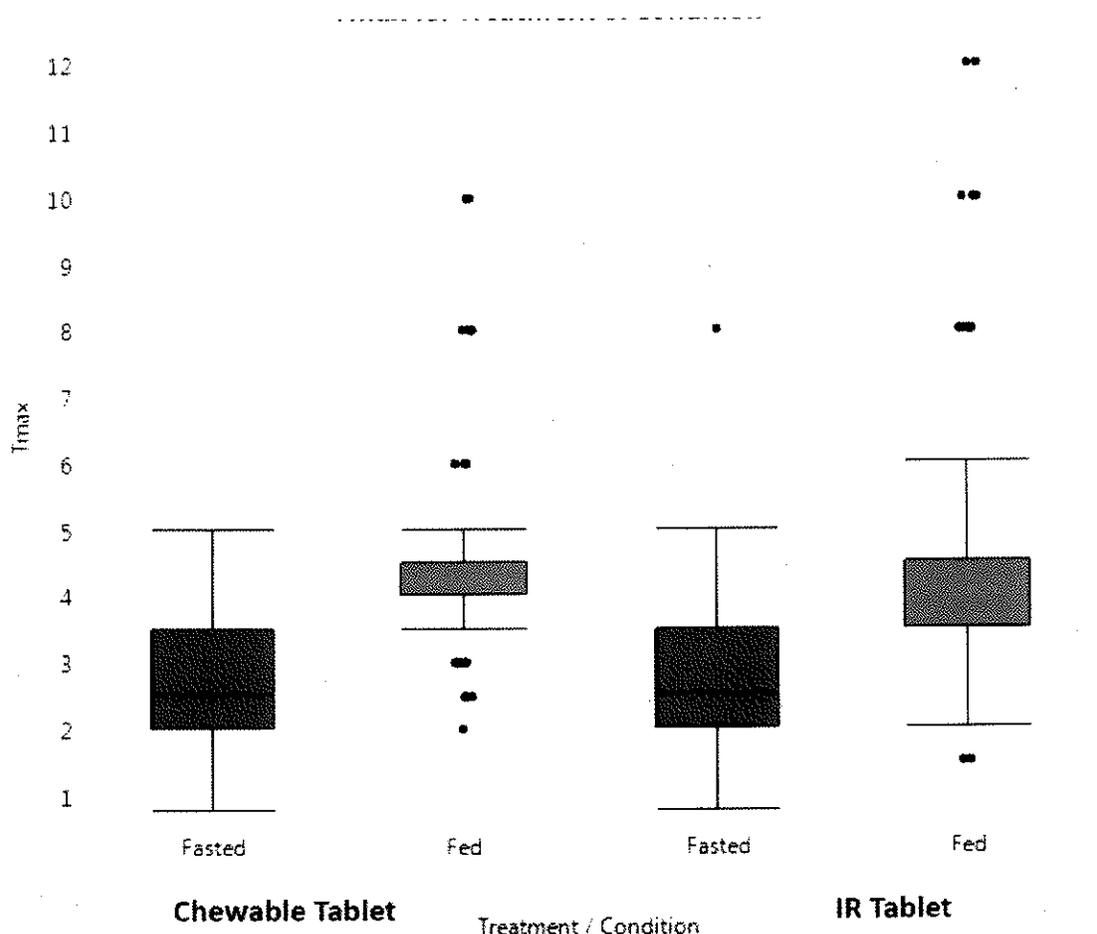
- 4. Please provide Summary Tables for the bioanalytical method validation and its performance in study #  $\text{(b) (4)}$ /13/187 using the attached template.*

## APPENDIX

PK parameters from the pivotal fasted and fed BE studies

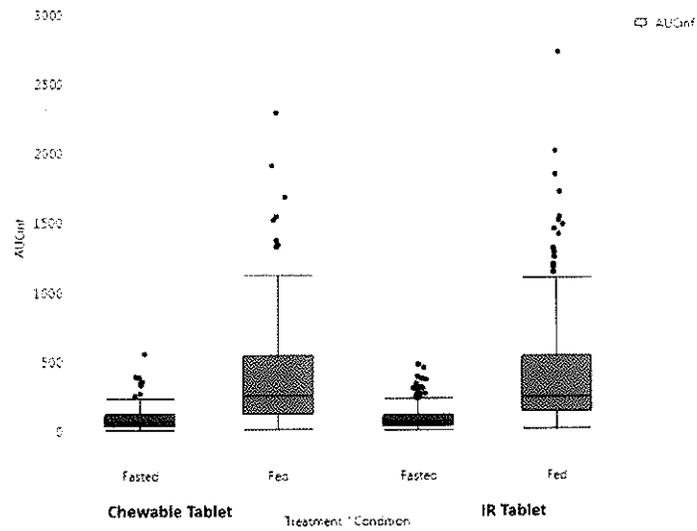


**Figure A1.** Comparison of albendazole  $T_{max}$  distribution in fasted (red) and fed (studies) for Albenza® and the proposed chewable tablets. Kolmogorov-Smirnov test (non-parametric test) indicated that there is not statistically significant difference between Chewable tablets and Albenza® in the fasted or fed group. However, there was a statistically significant difference between fasted and fed groups for both chewable tablets and Albenza®. The table summarized median (range) and mean of albendazole  $T_{max}$ .



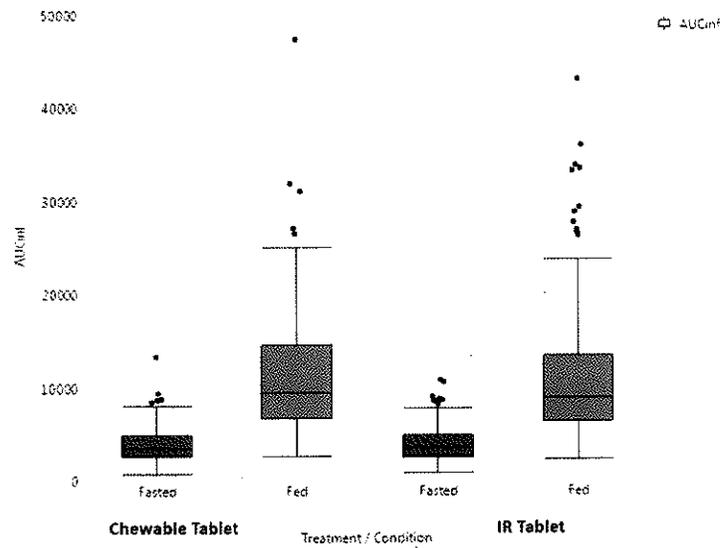
	Treatment / Condition			
	Chewable Tablets		IR Tablets	
	Fasted	Fed	Fasted	Fed
Median	2.5 (0.75-5)	4.5 (2-10)	2.5 (0.75-5)	4.5 (1.5-12)
Mean	2.8	4.5	2.8	4.3

**Figure A2.** Comparison of albendazole sulfoxide Tmax distribution in fasted (red) and fed (studies) for Albenza® and the proposed chewable tablets. Kolmogorov-Smirnov test (non-parametric test) indicated that there is not statistically significant difference between Chewable tablets and Albenza® in the fasted or fed group. However, there was a statistically significant difference between fasted and fed groups for both chewable tablets and Albenza®. The table summarized median (range) and mean of albendazole sulfoxide Tmax.



	Chewable Tablets		IR Tablets	
	Fasted	Fed	Fasted	Fed
Median	62	245	64	232
Mean	91 (0.6-552)	405 (8-2293)	86 (1-478)	463 (8-3818)

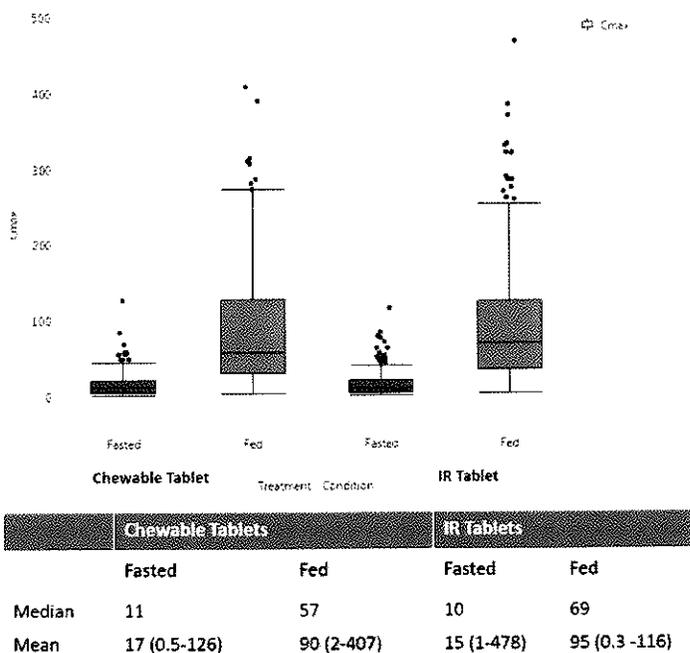
**Figure A3.** The distribution of albendazole AUC in the fed and fasted conditions for the proposed chewable tablets and Albenza®.



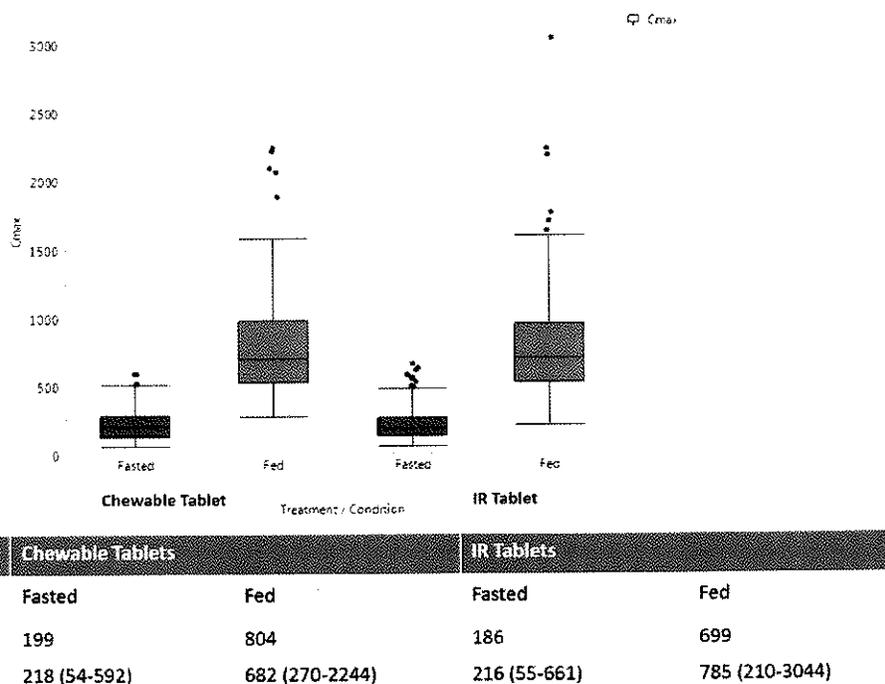
	Chewable Tablets		IR Tablets	
	Fasted	Fed	Fasted	Fed
Median	3075	3411	3255	3508
Mean	3485 (632-9507)	3878 (656-13363)	3506 (651-10714)	3802 (675-10828)

**Figure A4.** The distribution of albendazole AUC in the fed and fasted conditions for the proposed chewable tablets and Albenza®.

proposed chewable tablets and Albenza®.



**Figure A5.** The distribution of albendazole Cmax in the fed and fasted conditions for the proposed chewable tablets and Albenza®.



**Figure A6.** The distribution of albendazole sulfoxide Cmax in the fed and fasted conditions for the proposed chewable tablets and Albenza®.

## CLINICAL PHARMACOLOGY REVIEW

<b>NDA(s): 207844</b>	Submission Date(s): June 19, 2014
<b>Drug</b>	ALBENZA
<b>Trade Name</b>	Albendazole
<b>OCP Reviewer</b>	Dakshina M. Chilukuri, PhD
<b>OCP Team Leader</b>	Philip M. Colangelo, PharmD, PhD
<b>OCP Division</b>	DCP4
<b>OND Division</b>	DAIP
<b>Sponsor</b>	AMEDRA
<b>Formulation</b>	Chewable tablet
<b>Indication(s)</b>	Treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, <i>Taenia solium</i> , and cystic hydatid disease of the liver, lung, and peritoneum caused by the larval form of the dog tapeworm, <i>Echinococcus granulosus</i>

### 1. EXECUTIVE SUMMARY

This NDA from Amedra Pharmaceuticals is for a new formulation, Albenza (albendazole) Chewable Tablets, 200 mg. Albenza Tablets, 200 mg is currently approved under NDA 20666 for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, *Taenia solium*, and cystic hydatid disease of the liver, lung, and peritoneum caused by the larval form of the dog tapeworm, *Echinococcus granulosus*.

Four bioequivalence studies were conducted in support of approval of this chewable tablet formulation. The studies were randomized, open-label, balanced, two-treatment, three-period, three-sequence, single dose, reference replicated, cross-over studies in healthy male and female subjects under fed and fasted conditions. The objective of the studies was to assess the bioequivalence between the test product (Albenza Chewable Tablets, 200 mg) and the corresponding reference product (the current approved Albenza Tablets, 200 mg). These studies were reviewed by Salaheldin Hamed, Ph.D., in the Office of New Drug Quality Assessment (ONDQA).

The applicant did not submit any new clinical pharmacology information with this NDA. A request for a biowaiver was submitted and this was reviewed by ONDQA-Biopharm reviewer. No new efficacy or safety studies in patients with either hydatid disease or neurocysticercosis have been conducted for the new formulation of Albenza Chewable Tablets.

### 2. RECOMMENDATIONS

No new clinical pharmacology was submitted by the applicant in this NDA and thus, the clinical pharmacology team has no additional comments on this submission pending agreement on the labeling.

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/s/  
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04/20/2015

PHILIP M COLANGELO  
04/21/2015