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RESEARCH**

APPLICATION NUMBER:

209570Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: *Approval*

NDA 209570

Review # 1

Drug Name/Dosage Form	Benznidazole Tablets*
Strength	100 mg and 12.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Chemo Research S.L.
US agent, if applicable	Exeltis USA, Inc.

* *No proprietary name approved at the time of this review*

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	December 29, 2016	All
Amendment (eCTD 008)	March 17, 2017	Biopharmaceutics, Drug Product
Amendment (eCTD 010)	April 3, 2017	Biopharmaceutics
Amendment (eCTD 013)	April 12, 2017	Drug Product, Process
Amendment (eCTD 015)	April 24, 2017	Drug Product, Process
Amendment (eCTD 017)	May 3, 2017	Drug Substance, Drug Product, EA
Amendment (eCTD 018)	May 4, 2017	Drug Product, Process
Amendment (eCTD 020)	May 22, 2017	Drug Substance, Drug Product, Process
Amendment (eCTD 022)	May 31, 2017	Process, Biopharmaceutics, Drug Product
Amendment (eCTD 024)	June 20, 2017	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Katherine Windsor	Benjamin Stevens
Drug Product	Yong Wang	Balajee Shanmugam
Process	Jiao Yang	Steven Frisbee
Microbiology*	Jiao Yang	Steven Frisbee
Facilities	Cassandra Abellard	Derek Smith
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	N/A
Laboratory (OTR)	Laura Pogue	N/A
Environmental Assessment**	Jim Laurenson	N/A
Application Technical Lead	Dorota Matecka	N/A

* *The microbiology aspects of the drug product are assessed in the Process Chapter*

** *EA is covered in the Drug Product Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	May 24, 2017 (Panorama)	Review by Katherine Windsor

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
preIND	118796	Pre-NDA meeting on September 30, 2016 (meeting minutes dated October 28, 2016 in DARRTS)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, benznidazole tablets. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on June 7, 2017. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality.

II. Summary of Quality Assessments

A. Product Overview

Benznidazole (BNZ) is an antiprotozoal agent, a derivative of N-benzyl 2-nitroimidazole. It has been adopted as a first choice in the treatment of Chagas disease in most endemic countries and is included in the WHO Essential Medicines List. Chagas disease, or American trypanosomiasis, is a zoonosis caused by the parasite *Trypanosoma cruzi* (a flagellated protozoan parasite). Chagas disease is considered by first among parasitic diseases in the Americas.

This NDA provides for benznidazole tablets, 100 mg and 12.5 mg, which are indicated in pediatric patients 2 to 12 years of age for the treatment of Chagas disease (American trypanosomiasis), caused by *Trypanosoma cruzi*.

Proposed Indication(s) including Intended Patient Population	Treatment of Chagas Disease in pediatric patients 2 to 12 years of age.
Duration of Treatment	Pediatric Patients 2 to 12 years of age: The total daily dose is 5 mg/kg to 8 mg/kg orally administered in two divided doses separated by approximately 12 hours for a duration of 60 days.
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	The 100 mg tablet is functionally scored to allow for splitting into one-half or one-quarter tablet portions to provide dosage less than 100 mg. The whole tablets (12.5 mg or 100 mg) or the split portion(s) of the 100 mg tablet may be ^{(b) (4)} made into slurry for immediate administration to pediatric patients.

B. Quality Assessment Overview

Benznidazole is an antiprotozoal agent, a derivative of N-benzyl 2-nitroimidazole. Benznidazole drug substance is yellowish, practically crystalline powder insoluble in water, sparingly soluble in acetone, and slightly soluble in methanol and ethanol. The chemistry manufacturing and controls information for benznidazole drug substance has been provided via a reference to DMF (b) (4) held by (b) (4). DMF (b) (4) was reviewed in support of this NDA and was found to be acceptable (review dated May 24, 2017, in Panorama). The drug substance specification, which includes a number of relevant quality attributes such as description, identification (by IR <197K>), water content (<921> Method I), melting point (<741>), loss on drying (<731>), residue on ignition (<281>), heavy metals (<231>), assay, related substances, residual solvents, and particle size, was found acceptable to be used in the proposed drug product. Comparative data were provided in the NDA for benznidazole drug substance batches manufactured by (b) (4) (used to make clinical supplies) and benznidazole batches manufactured by the proposed drug substance commercial manufacturer, (b) (4). Comparative data included batch analysis results, physical characterization, and pH solubility profiles for three batches of drug substance manufactured at each site. Based on the evaluation of these data, the two drug substances sourced from (b) (4) were found comparable. Stability data from the DMF holder support a retest period of (b) (4) for benznidazole drug substance manufactured at (b) (4) and stored at (b) (4).

The drug product, benznidazole tablets, is supplied in two strengths, 100 mg and 12.5 mg. Benznidazole tablets, 100 mg, are round white tablets, about 10 mm diameter long, and scored twice in cross on both side and debossed with an “E” on one side on each split portion. Benznidazole tablets, 12.5 mg, are round, white tablets, about 5 mm and debossed with and “E” on one side. The whole 12.5 mg tablets or the split portions of the 100 mg tablets may be (b) (4) made into slurry for administration in pediatric patients who cannot swallow an intact tablet. The inactive ingredients include pregelatinized corn starch, monohydrate lactose, sodium croscarmellose, microcrystalline cellulose, magnesium stearate, (b) (4). All the excipients used in the manufacture of benznidazole tablets, 100 mg and 12.5 mg, meet the USP/NF specifications.

The drug product specification includes tests and acceptance criteria for appearance, identification, uniformity of dosage units, assay, dissolution, disintegration time, degradation products, microbial limits, (b) (4) content. During the review, several revisions to the proposed drug product specification were recommended by reviewers such a revision of the proposed acceptance criterion for dissolution (as discussed below), shortening of the proposed disintegration time, inclusion of the test for (b) (4) content and inclusion of content uniformity (b) (4) in the uniformity of dosage forms test for benznidazole tablet, (b) (4). In addition, the listing of impurities was revised to follow nomenclature recommended by the ICH Q3B guidance. The potential impurities in the drug product include (b) (4).

degradation studies of the drug products showed no sign of degradation; therefore, no specified impurities are listed in the drug product specification. The drug product specification, as revised, was found to be adequate. The analytical methods are described in reasonable detail and adequate validation data have been provided. The assay, chromatographic purity and dissolution analytical procedures were evaluation by the FDA laboratory and found acceptable.

Batch analysis data were provided for batches of benznidazole tablets manufactured using the drug substance supplied by (b) (4) (used to make clinical supplies) and benznidazole drug substance manufactured by (b) (4) (the proposed commercial manufacturer). The results of comparative release and three-month stability testing for these batches did not demonstrate significant differences in any of the quality attributes tested thus indicating that the quality of benznidazole drug substance sourced from the two suppliers is comparable.

The commercial drug product packaging container closure systems include white, high-density polyethylene (HDPE), white, opaque plastic bottles, which do not include a silica gel desiccant (b) (4). The 100 mg and 12.5 mg tablets are packaged into 70 mL and 35 mL HDPE bottles, respectively, each containing 100 tablets. The proposed container closure systems were found to be safe and suitable to store and protect the drug products, benznidazole tablets, 12.5 mg and 100 mg.

Stability of the proposed drug product, benznidazole tablets, 100 mg and 12.5 mg, packaged in the proposed commercial packaging configurations has been demonstrated through adequate 12-month stability data under 25°C/60% RH, and it was further supported by 9 and 6 months of stability results under 30°C/75% RH and at 40°C/75% RH, respectively. No obvious trends and no out of specification results were observed. Therefore, the proposed expiry dating of 24 month shelf-life for benznidazole tablets, 100 mg and 12.5 mg, packaged in bottles and to be stored at room temperature has been found acceptable.

The manufacturing process for the drug product, benznidazole tablets, consists of the followings steps: (b) (4)

(b) (4)

(b) (4) Overall, information regarding the drug product manufacturing process provided in the original NDA submission and subsequent amendments has been found acceptable.

From the biopharmaceutics perspective, benznidazole exhibits low solubility across the physiologic pH range. Both tablets, 100 mg and 12.5 mg, exhibit (b) (4) dissolution ((b) (4) % dissolves in 15 minutes) in 900 mL media with pH across the physiologic range, using the method parameters of the dissolution testing procedure. The proposed dissolution method and the acceptance criteria, as revised per the FDA recommendation

(Q = ^(b)₍₄₎% at 15 min), have been found acceptable for the routine release and stability testing of the whole tablet for the 100 mg and 12.5 mg strengths, as well as for the split portions of the 100 mg functionally-scored tablets. In addition, in vitro dissolution profiles provided for the drug product batches manufactured with benznidazole sourced from ^(b)₍₄₎ and the proposed commercial drug substance manufacturer ^(b)₍₄₎ were found comparable, thus further supporting the quality and comparability of the benznidazole drug substances derived from the two sources.

The Applicant's claim of categorical exclusion from the Environmental Assessment per 21 CFR 25.31(b), as revised and amended during the NDA review, has been found acceptable.

During the labeling review a number of revisions were recommended from the product quality perspective, such as the revision of the established name for the drug product, benznidazole tablets, and inclusion of appropriate storage conditions in the container label. In addition, the description of slurry preparation was revised to include details such as the amount of water to be used. The labels and package insert are currently under review by the NDA review team.

The benznidazole drug substance manufacturer is by ^(b)₍₄₎, and the drug product manufacturer is by Laboratorios Liconsa S.A., Spain. In addition, microbiological testing of the drug substance, excipients and the drug product is performed at the ^(b)₍₄₎

Based on the review of the application and inspectional documents for all manufacturing sites listed in this NDA, it has been determined that there are no significant outstanding issues with the facilities involved in the manufacturing of the proposed product. Therefore, the overall recommendation of "Approve" was entered into Panorama for this NDA by OPF on June 7, 2017.

C. Special Product Quality Labeling Recommendations (see labeling review)

D. Final Risk Assessment (see Attachment I)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Biopharmaceutics

CHAPTER V: Facilities

CHAPTER VI: Labeling

ATTACHMENT I: Risk Assessment

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BIOPHARMACEUTICS

Product Background:

NDA: 209570

Submission Type: 505(b)(1) NDA

Drug Product Name / Strength: (b) (4) (benznidazole) Tablet, 100 mg and 12.5 mg

Route of Administration: oral as whole or split portions of the tablet, or as slurry of the (b) (4) tablet in water (administered without regard to food)

Applicant Name: Chemo Research, S.L.

Background:

The Applicant is seeking approval of benznidazole oral tablets (100 mg and 12.5 mg strengths) for the treatment of Chagas’ disease in (b) (4) pediatric patients, pursuant to Section 505(b)(1) of the Food Drug and Cosmetics Act. There are currently no approved benznidazole drug products in the USA. The Applicant conducted two relative bioavailability studies to investigate (1) the oral bioavailability of the proposed tablet when administered intact/whole or as a slurry in water, and (2) food-effect. The PK data generated in these two relative BA studies will be compared to the historical PK data for the formulations (e.g., Radanil® or Rochagan® and the LAFEPE tablets) that were used in the medical literature studies that evaluated the efficacy of safety of oral benznidazole tablets in Chagas’ patients. Refer to the Clinical Pharmacology Review for the adequacy of this PK bridge between the proposed drug product and the literature drug product(s).

Review Summary:

Per BCS criteria, benznidazole exhibits low solubility across the physiologic pH range. Both 100 mg and 12.5 mg strengths of the proposed drug product exhibit (b) (4) dissolution (b) (4)% (dissolves in 15 minutes) in 900 mL media with pH across the physiologic range, using the method parameters as proposed for QC dissolution testing.

For the routine QC testing of the whole tablets of the 12.5 mg and the 100 mg benznidazole strengths, as well as the split portions of the 100 mg functionally-scored tablet, at batch release and during stability testing, the following proposed dissolution method and the revised acceptance criterion as shown in the table below, are found acceptable.

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddles)	75 rpm	0.1N HCl (pH 1.0), 37 ± 0.5 °C	900 mL	Q = (b) (4)% at <u>15 min</u>

Using the above QC dissolution method, the half-split and quarter-split portions of the 100 mg tablet also exhibited (b) (4) *in vitro* dissolution.

In vitro and/or *in vivo* bridging data (between formulations of the proposed drug product) *per se* are not needed, since both strengths of the benznidazole tablet, manufactured using the proposed commercial formulation/manufacturer, were evaluated in two relative bioavailability studies conducted by the Applicant.

Overall, the comparative data for clinical PK, *in vitro* dissolution profiles, and drug substance solubility in various pH media suggest the equivalence of the drug product batches manufactured with the APIs sourced from either the (b) (4) (b) (4) or the proposed commercial drug substance manufacturer (b) (4) (b) (4).

List Submissions being reviewed (table):

SDN-1, 12/29/2016 (Original NDA)

SDN-8, 3/17/2017 (Response to Quality Information Request)

SDN-10, 4/3/2017 (Response to Quality Information Request)

SDN-13, 4/10/2017 (Response to Quality Information Request (e.g., polymorphism, disintegration))

SDN-15, 4/24/2017 (Response to Quality Information Request (e.g., (b) (4) content))

SDN-18, 5/4/2017 (Response to Quality Information Request (b) (4) particle size distribution)

SDN-22, 5/31/2017 (Response to Quality Information Request (e.g., dissolution acceptance criterion))

Highlight Key Outstanding Issues from Last Cycle:

Not Applicable

Concise Description Outstanding Issues Remaining:

None

BCS Designation**Reviewer's Assessment:**

The Applicant did not formally request a BCS designation for (b) (4) (benznidazole) oral tablets, but considers the API to exhibit the characteristics of a (b) (4) drug substance, however, this Reviewer does not agree with this classification because, as shown below, per BCS criteria, this Reviewer considers benznidazole as a *low-solubility* drug substance.

(b) (4)

Permeability: The absolute bioavailability of orally administered (b) (4) (benznidazole) oral tablets is not known. The proposed labeling of (b) (4)

(b) (4)

(b) (4)

Dissolution: In 900 mL (b) (4) pH buffer solutions (pH 1.0 0.1N HCl, (b) (4) (b) (4), both 12.5 mg and 100 mg strengths of the proposed drug product exhibited (b) (4) dissolution (b) (4) % dissolves in 15 min), using USP Apparatus II (paddle) rotating at 75 rpm; see Section 4.2.2 of API Comparability Report [LPRI747-DOC008](#) in 3.2.R. The

(b) (4)

Dissolution Method and Acceptance Criteria**Reviewer's Assessment:**

Per BCS criteria, this Reviewer considers benznidazole as a *low-solubility* drug substance. Both 12.5 mg and 100 mg strengths of the benznidazole oral tablets exhibit (b) (4) dissolution (i.e. (b) (4) % dissolution within 15 min) when using the proposed QC dissolution method parameters, i.e., USP dissolution 2 (paddle) rotating at 75 rpm, with 900 mL media [including 0.1N HCl (QC medium), (b) (4)]

Dissolution Method – ADEQUATE

For routine QC at batch release and during stability testing of both 12.5 mg and 100 mg strengths of the whole tablets and the half-split and quarter-split portions of the functionally scored 100 mg tablet, the proposed QC dissolution method consists of USP Apparatus 2 (paddle) rotating at 75 rpm, 900 mL of 0.1N HCl (pH 1.0) at 37°C.

(b) (4)

Discriminating Power

The Applicant evaluated the discriminating power of the proposed QC dissolution method for changes in manufacturing process variables and changes in drug product composition, using both 12.5 mg and 100 mg strengths. It was demonstrated that the proposed QC dissolution method was able to detect (b) (4) (Figures 1 through 3).

However, at the studied ranges, the proposed QC dissolution method was not able to detect

(b) (4)

Figure 1

(b) (4)

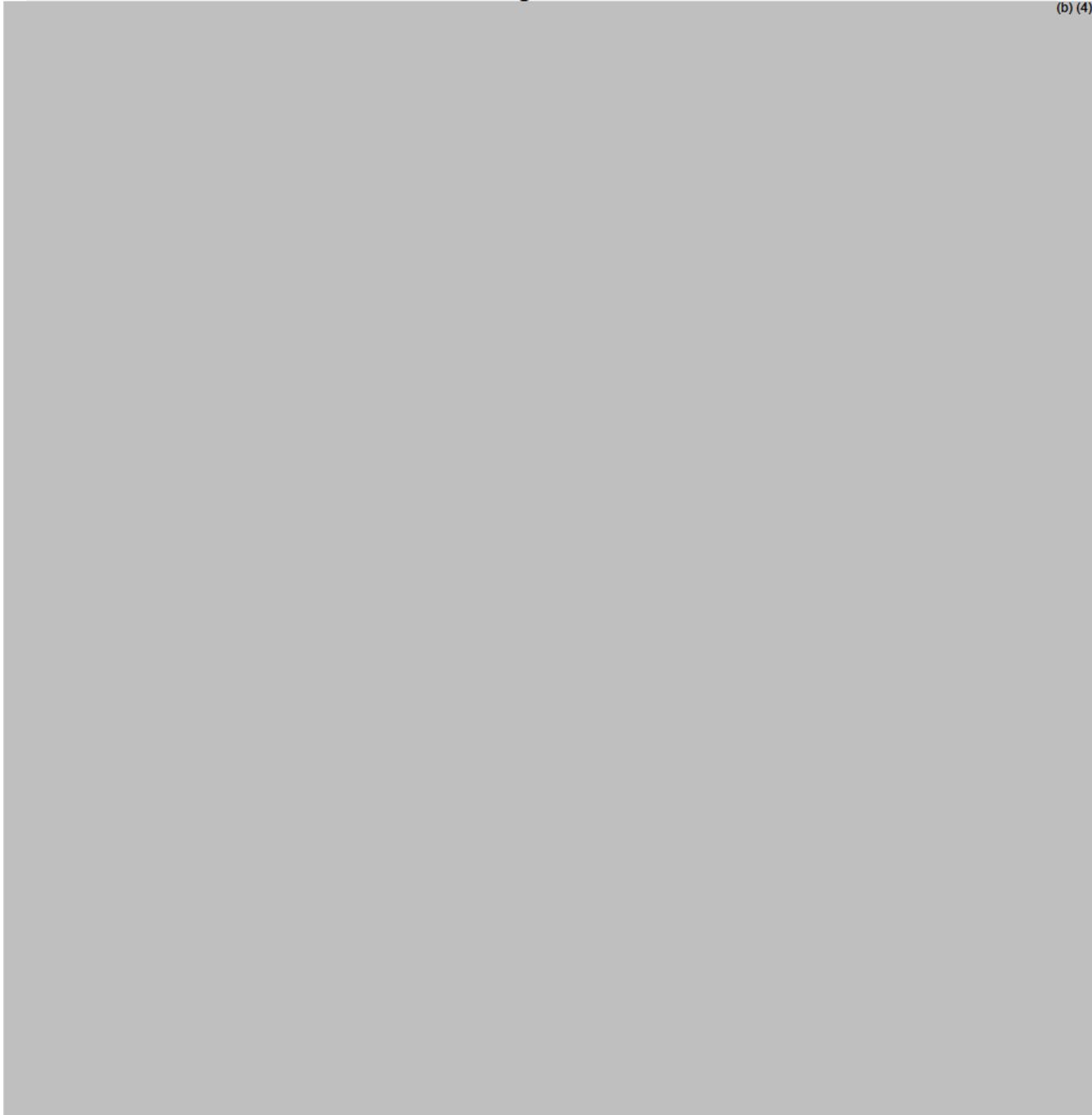


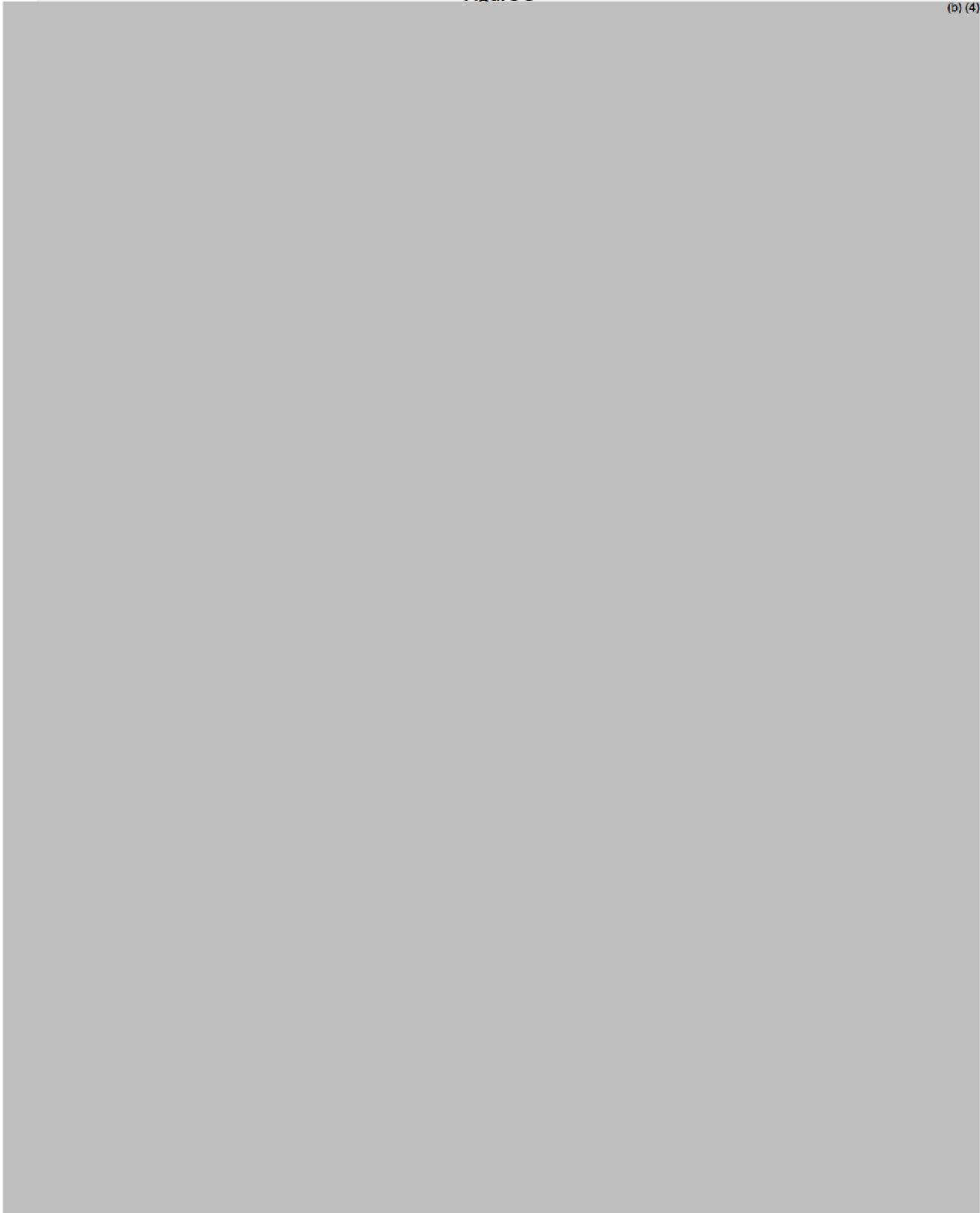
Figure 2

(b) (4)



Figure 3

(b) (4)





Dissolution Acceptance Criteria – ADEQUATE

For batch release and stability testing, the proposed QC dissolution acceptance criterion is 'Q =

(b) (4)

(b) (4)

(b) (4) The Applicant considers 'Q =

(b) (4)

(b) (4)

. The Applicant notes that dissolution data at (b) (4) min were provided in the Certificates of Analyses of the bio-batches. A dissolution acceptance criterion of 'Q (b) (4)% in (b) (4) min' was used for the release of the clinical batches used in the Relative BA studies conducted for the to-be-marketed drug product.

This Reviewer recommends that the proposed dissolution acceptance criterion be (b) (4)

(b) (4) 'Q (b) (4)% at 15 min' based on the dissolution profile data provided for the whole 12.5 mg and 100 mg strengths of the bio-batches (or batches manufactured from the same parent batch) at the time of batch release, and considering the dissolution profile data provided for the bio-batches and other stability batches (manufactured using the

proposed commercial source API) at the current (15-month) long-term stability data time point). Additionally, the Reviewer's recommendation considers that the intentionally manufactured deviant batches

(b) (4)

(b) (4)

(b) (4) as the specification time point for $Q = \frac{(b) (4)}{(4)}\%$.

The mean dissolution rate of the split tablet portions was comparable (b) (4) than the whole tablet, so the same recommended dissolution acceptance criterion applies for the dissolution testing of the split portions of the functionally scored 100 mg tablet. The comparative *in vitro* dissolution profiles of the split tablet portions relative to the whole tablet are supportive of the "functional score" of the 100 mg tablet; refer to the Drug Product Review for the evaluation of the split tablet portions with respect to conformance to the other quality attributes in the proposed QC specifications the whole 100 mg tablets.

Dissolution on Stability

Dissolution data at (b) (4) min were provided for the drug product batches used in the relative bioavailability (BA) studies and stability testing. The recommended storage of the drug product is at controlled room temperature 20° to 25°C. As reported by the Applicant, the stability samples conformed to the proposed dissolution acceptance criterion ($Q = \frac{(b) (4)}{(4)}\%$ at (b) (4) min) up to 6 months of accelerated, up to 9 months of intermediate, and up to 9 and 18 months (for the product using (b) (4) API and (b) (4) API, respectively) of long-term storage when tested as whole 100 mg and 12.5 mg tabs (by Stage 1) and also as half- and quarter- split portions of the 100 mg tablets (by Stage 2).

Based on the *in vitro* dissolution profile data provided at the current long-term (25°C/60%RH) stability time point, all registration (stability) batches except the Relative BA Study LPRI747-101 bio-batch produced using (b) (4) API exhibited (b) (4) dissolution (b) (4) % dissolved in 15 min). Specifically, at the 15 min and 20 min sampling time points, the mean (%RSD; range) dissolution of 12 units of Batch DG1501527 were (b) (4) % and (b) (4) %, respectively, when stored for 25 months at 25°C/60%RH. All six other stability batches (DG1501746 to 48 for 100 mg; DG1501723, DG1501724, DG1501749) produced using (b) (4) sourced API, showed (b) (4) % dissolution as early as the 15 min sampling time point at 15 months of long-term storage. Of note, the proposed commercial source of the API is (b) (4) (not (b) (4)). Note also that Bio-batch DG1501528 (which comes from the same Parent Batch as (b) (4) Batch DG1501527) was approximately 5 months old when used in the Relative BA Study LPRI747-101, whereas Bio-batches DG1501748 (100 mg) and DG1501724 (12.5 mg) were 7 months old and 9 months old, respectively, when used in the Study LPRI747-102.

The proposed shelf-life is 24 months, when packaged in a high-density polyethylene bottle with a (b) (4) cap. Refer to the Drug Product Review for the acceptability of the proposed expiration dating period.

Pediatric Dosing

The proposed *alternative* mode of administration for pediatric dosing of the tablets is to prepare a slurry using a small volume of water onto a cup; the slurry will be orally administered immediately, (b) (4). Note that in the relative BA study conducted by the Applicant, the initial volume of water used was 80 mL followed by two rinses with 80 mL each.

(b) (4)

Refer to the Drug Product Review for the evaluation of the quality aspects of the slurry as relevant to pediatric dosing, and the acceptability of the proposed (b) (4) acceptance criteria (b) (4) in the Finished Drug Product Specifications.

Biowaiver Request**Reviewer's Assessment: NOT APPLICABLE**

A request to waive the requirement to conduct *in vivo* BA studies was not submitted nor required. Both 12.5 mg and 100 mg tablets were evaluated in the conducted Relative Bioavailability Study LPRI747/102; the 100 mg strength was tested in the Food-Effect Study LPRI 767/101. The two proposed strengths do not appear to be (b) (4) to each other because the total additive effect of the excipient differences is (b) (4)%; however, PK data are available for both strengths of the tablet.

Bridging of Formulations**Reviewer's Assessment: NOT APPLICABLE**

Bridging data between formulations of the proposed drug product *per se* are not needed because both strengths of the to-be-marketed tablet produced by the proposed commercial manufacturer [Liconsa (Spain)] were used in Applicant-conducted PK Studies, i.e., to evaluate food-effect LPRI 767/101; (100 mg; Batch DG1501528), and the effect of administration as slurry (LPRI747/102), 1 x 100 mg tablet (whole or crushed [DG1501748-A] as slurry in 3 x 80 mL water), 8 x 12.5 mg tablet crushed as slurry [Batch DG1501724-A]) under fasted conditions.

Note that the 100 mg and 12.5 mg tablet batches tested in Relative BA Study LPRI747/102 were manufactured using the API from the proposed commercial drug substance source (b) (4) (b) (4), and has the proposed Appearance of the to-be-marketed tablets (i.e., with proposed commercial debossing). On the other hand, the 100 mg tablets used in Food-Effect

Study LPRI 767/101 were manufactured using the API sourced from (b) (4). That the benznidazole PK parameters were comparable between the 100 mg bio-batches used in Studies LPRI 767/101 and LPRI747/102 (as confirmed by the Clinical Pharmacology Reviewer, Dr. Abhay Joshi) indicates the equivalence of the API from the original source (b) (4) and the proposed commercial source (b) (4).

Additionally, comparative *in vitro* dissolution profile data were provided to support the API supplier change [from (b) (4) to (b) (4)]; see 3.2.R.2.S and 3.2.R.2.P (comparability protocols), Report LPRI747-DOC008. Based on the data provided in this report and at the current stability time point, the (b) (4) *in vitro* dissolution profile of the drug product batches manufactured using (b) (4)-sourced API is comparable to (and appears to be slightly more stable during long-term storage) than the drug product batch manufactured using the (b) (4)-sourced API.

Note: The Applicant proposes to bridge to the efficacy and safety information in published clinical trials based on the demonstration of comparable benznidazole PK of the proposed to-be-marketed drug product (of Chemo Research, Ltd) to historical PK data in literature studies using either Radanil® (aka Rochagan®), or the benznidazole tablet manufactured by Laboratório Farmaceutico do Estado de Pernambuco (LAFEPE), Brazil. Note that the Roche® product was used in the pediatric PK literature studies whereas the LAFEPE product was used in published/unpublished adult PK and pediatric (population) PK studies; refer to the Clinical Pharmacology review of Dr. Joshi for the evaluation of the adequacy of PK bridging from these reference products to the NDA product. Of note, the Applicant indicated that since the Roche and the LAFEPE benznidazole tablets are no longer commercially available or cannot be procured, comparative *in vitro* testing of these two reference drug products cannot be conducted.

List of Deficiencies:

None

Recommendation: From the Biopharmaceutics perspective, NDA 209570 for

(b) (4) (benznidazole) Tablets, 100 mg and 12.5 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD. (5/25/2017)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): I concur with Dr. Gieser's assessment and recommendation. Elsbeth Chikhale, PhD (5/26/2017)



Gerlie
Gieser

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LABELING

[IQA Review Guide Reference](#)

NDA 209570

1. Package Insert

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)

(b) (4) (benznidazole) tablets, for oral use

Initial U.S. Approval: 20XX

-----INDICATIONS AND USAGE-----

(b) (4) a nitroimidazole (b) (4) indicated for the treatment of Chagas disease. (1)

(b) (4)

-----DOSAGE FORMS AND STRENGTHS-----

- (b) (4) tablets (scored) tablets, 100 mg (3, (b) (4))
- (b) (4) tablets, 12.5 mg (3, (b) (4))

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	(b) (4)
Proprietary name and established name	(b) (4) (benznidazole)
Dosage form, route of administration	(b) (4) (benznidazole) tablets, for oral use
Controlled drug substance symbol (if applicable)	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	<ul style="list-style-type: none"> • (b) (4) tablets (scored) tablets, 100 mg (3, (b) (4)) • (b) (4) tablets, 12.5 mg (3, (b) (4))

2. Section 2 Dosage and Administration

2 DOSAGE AND ADMINISTRATION

(b) (4) tablets are for oral use and may be taken with or without food. (b) (4) dosed by (b) (4) body weight (kg). The total daily dose (b) (4) administered in two divided doses (separated by approximately 12 hours), (b) (4) for 60 days.

(b) (4)

(b) (4) tablets may be made into a slurry in water for the pediatric population with (b) (4) body weight. The slurry is prepared by the following method:
 The contents of the cup (b) (4) tablet with water) (b) (4) immediately (b) (4) (b) (4). Rinse the cup with water (b) (4).

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4) tablets may be made into a slurry in water for the pediatric population with (b) (4) body weight. The slurry is prepared by the following method: The contents of the cup (b) (4) tablet with water) (b) (4) immediately (b) (4). Rinse the cup with water (b) (4). (b) (4)

Reviewer's Assessment of Package Insert: *Inadequate*

On March 25, 2017 the following information was recommended from the applicant.

Provide a detailed description of slurry preparation (listed in the proposed package insert) and include the recommended amounts of water for slurry preparation and rinse along with a justification.

On 25 May 2017, the applicant provided instructions for slurry preparation for (b) (4) tablet, (b) (4).

(b) (4)

Refer to DMEAP's review for more comments.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Section 3 Dosage Forms and Strengths

(b) (4) tablets are available in 100 mg and 12.5 mg tablets (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	100 mg and 12.5 mg
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	To be included (refer to following comment)

Reviewer’s Assessment of Package Insert: *Adequate*

For section 3 Dosage Forms and Strengths, the following was recommended to the applicant on May 26, 2017.

(b) (4) (benznidazole) tablets are available as 100 mg and 12.5 mg tablets.

The 100 mg white tablets are round and functionally scored twice as a cross on both sides debossed with “E” on one side of each quarter portion.

The 12.5 mg white tablets are round and unscored debossed with “E” on one side.

Section 11 Description

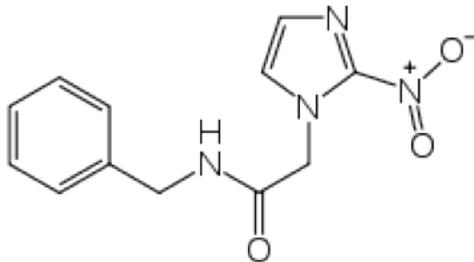
11 DESCRIPTION

(b) (4) tablets are white round tablets each containing 12.5 mg or 100 mg of benznidazole. The 100 mg white tablets are round and (b) (4) scored. (b) (4) debossed with “E” on one side of each quarter portion.

The 12.5 mg white tablets are round and (b) (4) debossed with “E” on one side.

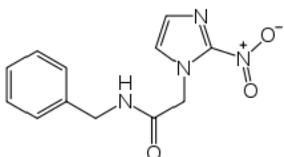
The inactive ingredients are as follows: Pregelatinized Corn Starch, NF, Monohydrate Lactose, NF, Sodium Croscarmellose, NF, Microcrystalline Cellulose, NF, and Magnesium Stearate, NF.

(b) (4) nitroimidazole (b) (4). The chemical name of benznidazole is N-benzyl-2-(2-nitro-1H-imidazol-1-yl) acetamide. The empirical formula is $C_{12}H_{12}N_4O_3$ and the molecular weight is 260.246 g/mol. The structural formula is:



(b) (4) is a yellowish, practically crystalline powder that is practically insoluble in water, sparingly soluble in acetone and ethanol, and slightly soluble in methanol.

APPEARS THIS WAY ON ORIGINAL

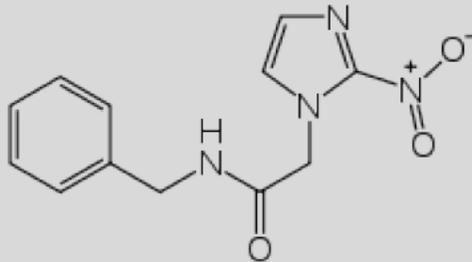
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	(b) (4) No established name is provided
Dosage form and route of administration	Tablets Route of administration is not available.
Active moiety expression of strength with equivalence statement (if applicable)	NA
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Pregelatinized Corn Starch, NF, Monohydrate Lactose, NF, Sodium Croscarmellose, NF, Microcrystalline Cellulose, NF, and Magnesium Stearate, NF.
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	(b) (4) (b) (4) nitroimidazole (b) (4)
Chemical name, structural formula, molecular weight	Benznidazole, C ₁₂ H ₁₂ N ₄ O ₃ , wt = 260.246 g/mol 
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	(b) (4) is a yellowish, practically crystalline powder that is practically insoluble in water, sparingly soluble in acetone and ethanol, and slightly soluble in methanol.

Reviewer's Assessment of Package Insert: Adequate

For section 11 DESCRIPTION, the following was recommended to the applicant on May 26, 2017.

(b) (4) tablets contain benznidazole, a nitroimidazole (b) (4). The chemical name of benznidazole is N-benzyl-2-(2-nitro-1H-imidazol-1-yl) acetamide.

The empirical formula is $C_{12}H_{12}N_4O_3$ and the molecular weight is 260.246 g/mol. The structural formula is:



Benznidazole is a yellowish, practically crystalline powder that is practically insoluble in water, sparingly soluble in acetone and ethanol, and slightly soluble in methanol.

(b) (4) (benznidazole) tablets are white round tablets each containing 12.5 mg or 100 mg of benznidazole, for oral use. The 100 mg white tablets are round and functionally scored twice as a cross on both sides debossed with “E” on one side of each quarter portion. The 12.5 mg white tablets are round and unscored debossed with “E” on one side.

The inactive ingredients are as follows: magnesium stearate, NF, microcrystalline cellulose, NF, monohydrate lactose, NF, pre-gelatinized corn starch, NF, and sodium croscarmellose, NF.

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) tablets (12.5 mg or 100 mg) are supplied (b) (4). Each white, round tablet (b) (4):

- 100 mg benznidazole (b) (4) “E” on one side of each quarter portion.
- 12.5 mg benznidazole (b) (4) with an “E” on one side.

(b) (4) 100 mg tablets -- NDC XXXX-XXXX-XX available in (b) (4)
(b) (4)

(b) (4) 12.5 mg tablets -- NDC XXXX-XXXX-XX available in (b) (4) of 100 tablets.

16.2 Storage and Handling

Store at controlled room temperature 20° to 25°C (68°to 77°F). Keep bottle tightly closed and protect from moisture. (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	
Available units (e.g., bottles of 100 tablets)	100 mg benznidazole 12.5 mg benznidazole
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	100 mg benznidazole (b) (4) (b) (4) an “E” on one side of each quarter portion. 12.5 mg benznidazole (b) (4) (b) (4) one side with an “E” on one side.
Special handling (e.g., protect from light)	NA
Storage conditions	Store at controlled room temperature 20° to 25°C (68°to 77°F). Keep bottle tightly closed and protect from moisture. (b) (4) (b) (4)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for Chemo Research, S. L., Madrid, Spain Manufactured by Laboratorios Liconsa S.A., Guadalajara, Spain Distributed by: Exeltis USA, Inc. Florham Park, NJ 07932

Reviewer’s Assessment of Package Insert: *Adequate*

For section 16 HOW SUPPLIED/STORAGE AND HANDLING, the following was recommended to the applicant on May 26, 2017.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

(b) (4) (benznidazole) tablets (12.5 mg or 100 mg) are supplied as follow:

The 100 mg white tablets, round and functionally scored twice as a cross on both sides. Each tablet is about 10 mm in diameter debossed with “E” on one side of each quarter portion.

12.5 mg white tablets, round and unscored. Each tablet is about 5 mm in diameter debossed with “E” on one side.

(b) (4) 100 mg tablets -- NDC XXXX-XXXX-XX available in bottles of 100 tablets.

(b) (4) 12.5 mg tablets -- NDC XXXX-XXXX-XX available in bottles of 100 tablets.

16.2 Storage and Handling

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Keep bottle tightly closed and protect from moisture. (b) (4)

(b) (4)

II. Labels:

1. Container Labels for Benznidazole Tablets, 12.5 mg and 100 mg

(b) (4)

1. Carton Label for Benznidazole Tablets, 12.5 mg and 100 mg

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: (b) (4) Established name: Benznidazole tablets The established name is at least half as large as the type property name. The font size, prominence, and layout are acceptable.	Proprietary name: (b) (4) Established name: Benznidazole tablets The established name is at least half as large as the type property name. The font size, prominence, and layout are acceptable.
Dosage strength	12.5 mg and 100 mg For oral use	12.5 mg and 100 mg For oral use
Net contents	100 tablets	100 tablets
“Rx only” displayed prominently on the main panel	“Rx only” is displayed prominently on the main panel.	“Rx only” is displayed prominently on the main panel.
NDC number (21 CFR 207.35(b)(3)(i))	The space for NDC number is available.	The space for NDC number is available.
Lot number and expiration date (21 CFR 201.17)	Lot number and expiry date are available.	Lot number and expiry date are available.
Storage conditions	Keep out of the reach of children. (The applicant needs to provide storage conditions)	Keep out of the reach of children. Store at controlled room temperature. 20° to 25°C (68° to 77°F). Keep bottle tightly closed and protect from moisture.
Bar code (21CFR 201.25)	The bar code is provided.	The bar code is provided.
Name of manufacturer/distributor	Manufactured for Chemo Research, S.L., Madrid, Spain Manufactured by Laboratorios Liconsa S.A., (b) (4) (b) (4) Guadalajara 19200, Spain Distributed by Exeltis USA, Inc., Florham Park, USA	Manufactured for Chemo Research, S.L., Madrid, Spain Manufactured by Laboratorios Liconsa S.A., (b) (4) (b) (4) Guadalajara 19200, Spain Distributed by Exeltis USA, Inc., Florham Park, USA
And others, if space is	See prescribing information for	See prescribing information

available	Dosage and Administration.	for Dosage and Administration.
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Reviewer’s Assessment of Labels: *Inadequate*

Deficiencies:

In the proposed container and carton labeling, add tablets after Benznidazole as “Benznidazole tablets, 12.5 mg” or Benznidazole tablets, 100 mg.

Provided storage conditions in container labels

List of Deficiencies:

1. In the proposed container and carton labeling, add tablets after Benznidazole as “Benznidazole tablets, 12.5 mg” or Benznidazole tablets, 100 mg.
2. Provided storage conditions in container labels.
3. (b) (4)
4. (b) (4)
5. Add (b) (4) after “...shake and gently to mix”.

Overall Assessment and Recommendation:

Upon completion of the above changes, the PI and container and carton labeling are acceptable from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Yong Wang 6/2/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):



Yong
Wang

Digitally signed by Yong Wang
Date: 6/05/2017 05:04:06PM
GUID: 508da7210002a01861739fd87b35adb9



Balajee
Shanmugam

Digitally signed by Balajee Shanmugam
Date: 6/05/2017 08:36:37PM
GUID: 50758d5000003c1b1962e036ea11002c

Addendum to the Labeling Review

NDA: 209570

Date: July 27, 2017

Subject: Package Insert; Section 2.3 Preparation of Slurry as Alternative Method of Administration

Section 2.3 Preparation of Slurry as Alternative Method of Administration was modified to include the use of 100 mg tablet in slurry preparation. This decision was made by the review team based on the relative bioavailability study conducted for this NDA, which included preparation of slurry as an alternate method of administration using both strengths of benznidazole tablets (100 mg and 12.5 mg tablets). In addition, slight modifications were made in the slurry preparation procedure for 12.5 mg tablets. Therefore, this addendum is to update the labeling review capturing the revisions under Section 2.3.

The updated version of Section 2.3, as revised, reads:

- A. Preparation of Slurry Using BENZNIDAZOLE TABLETS 12.5 mg (b)(4) for the Pediatric Population with (b)(4) Body Weight (Less Than 30 kg)

BENZNIDAZOLE TABLETS 12.5 mg tablets may be made into a slurry in a specified volume of water for the pediatric population with (b)(4) body weight (see Table 2). The 12.5 mg tablet slurry is prepared by the following method:

Table 2: Preparation and Administration of Slurry Using BENZNIDAZOLE TABLETS 12.5 mg (b)(4) for the Pediatric Population with (b)(4) Body Weight of Less than 30 Kg			
<ul style="list-style-type: none">Place the prescribed dose of BENZNIDAZOLE TABLETS 12.5 mg tablets into a cup.Add the specified volume of water per number of 12.5 mg tablets as shown below.			
Body Weight Range (kg)	Dose (mg)	Number of BENZNIDAZOLE TABLETS 12.5 mg	Quantity of Water for Preparing the Slurry
Less than 15 kg	50 mg	4 tablets	40 mL
15 kg to less than 20 kg	62.5 mg	5 tablets	50 mL
20 kg to less than 30 kg	75 mg	6 tablets	60 mL
<ul style="list-style-type: none">Allow the tablets to disintegrate in the cup over a period of approximately 1-2 minutes.Shake the contents of the cup gently to mix.Drink the contents of the cup (slurry of tablets with water) immediately.Rinse the cup with an additional 10 mLs of water and drink the whole amount.			

B. Preparation of Slurry Using BENZNIDAZOLE TABLETS 100 mg (b) (4) for the Pediatric Population with (b) (4) Body Weight (30 kg or greater)

BENZNIDAZOLE TABLETS 100 mg (b) (4) can be made into a slurry in a specified volume of water for the pediatric population with (b) (4) body weight (30 kg or greater) (see Table 3). The 100 mg tablet slurry is prepared as follows:

Table 3: Preparation and Administration of Slurry Using BENZNIDAZOLE TABLETS 100 mg (b) (4) for the Pediatric Population with (b) (4) Body Weight (30 kg or greater)			
<ul style="list-style-type: none">Place the prescribed dose of BENZNIDAZOLE TABLETS 100 mg tablets into a cup.Add the specified volume of water per number of 100 mg tablets as shown below.			
Body Weight Range (kg)	Dose (mg)	Number of BENZNIDAZOLE TABLETS 100 mg	Quantity of Water for Preparing the Slurry
30 kg to less than 40 kg	100 mg	1 tablet	80 mL
40 kg to less than 60 kg	150 mg	1 ½ tablets	120 mL
Greater than or equal to 60 kg	200 mg	2 tablets	160 mL
<ul style="list-style-type: none">Allow the tablet(s) to disintegrate in the cup over a period of approximately 1-2 minutes.Shake the contents of the cup gently to mix.Drink the contents of the cup (slurry of tablet(s) with water) immediately.Rinse the cup by adding 80 mLs of water and drink the whole amount.			

Reviewer Comments: Based on discussions with the review team and results of slurry preparations, the updated content of Section 2.3 Preparation of Slurry as Alternative Method of Administration is acceptable from a CMC perspective.



Yong
Wang

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Balajee
Shanmugam

Digitally signed by Balajee Shanmugam
Date: 8/11/2017 11:03:09AM
GUID: 50758d5000003c1b1962e036ea11002c

ATTACHMENT I: Final Risk Assessment

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability of benznidazole	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate specification for the drug substance	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	L	Uniformity of dosage form test in the DP spec for 12.5 mg tablets was revised to include content uniformity by assay	Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	L	The most stable DS (b) (4) is Data provided to show that no conversion occurs during DP manufacture	Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	L	Microbial limits testing conducted at (b) (4)	Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	L	The dissolution method was found adequate; the acceptance criterion for drug product release and stability test was revised	Acceptable	
Disintegration	Formulation Raw materials Process parameters Scale/equipment Site	L	Acceptance criterion was revised based on available data	Acceptable	

