

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209570Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209570	NDA Supplement #: N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Pending Established/Proper Name: Benznidazole Dosage Form: Tablet Strengths: 100 mg and 12.5 mg		
Applicant: Chemo Research, S.L.		
Date of Receipt: December 29, 2016		
PDUFA Goal Date: August 29, 2017		Action Goal Date (if different): Same
RPM: Gregory DiBernardo		
Proposed Indication: Treatment of Chagas disease		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	To support clinical safety and effectiveness, studies published in literature are being used. To support nonclinical safety both literature and stand-alone nonclinical are being used. Based on the bioavailability information described in a different literature (Raaflaub and Ziegler, 1979), a PK bridge between the product used in the aforementioned published studies (that are being used to support clinical safety and effectiveness) and the proposed products was established. See also question 3 below.

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

In the published studies, upon which the Applicant is relying to support clinical safety and effectiveness, the formulation used was the 100 mg benznidazole formulation known as Radanil[®] (manufactured by Hoffman-LaRoche), which was previously marketed outside of the United States. Given the Radanil[®] formulation is no longer commercially available and none of the proposed formulations (i.e., 100 mg and 12.5 mg benznidazole tablets) were used in the clinical trials providing evidence of safety and effectiveness, the Applicant has provided an exposure bridge. The exposure bridge is relying on the findings from Report LPRI747-DOC006, which provides a cross-study historic comparison of the benznidazole bioavailability from the Radanil[®] (reported by Raaflaub and Ziegler, 1979) and the single dose administration of the proposed tablet formulations, which were evaluated by the Applicant in the two submitted clinical pharmacology studies (LPRI 747/101 and LPRI 747/102).

RELIANCE ON PUBLISHED LITERATURE

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

If “NO,” proceed to question #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If “NO” to (a) proceed to question #11.

If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If “**NO**”, proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

GREGORY F DIBERNARDO
08/28/2017

MAUREEN P DILLON PARKER
08/28/2017

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # 209570
PMR/PMC Set (####-#) 3247-1
Product Name: Benznidazole tablets
Applicant Name: Chemo Research SL
ODE/Division: OAP/DAIP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a prospective, single-arm, multicenter trial, with historical controls, to evaluate safety, efficacy and pharmacokinetics of benzindazole tablets for treatment of Chagas disease in children.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	11/2017
Final Protocol Submission:	03/2018
Interim pharmacokinetics report:	12/2018
Interim trial report:	12/2021
Trial Completion:	12/2025
Final Report Submission:	05/2026

SECTION C: PMR/PMC Rationale

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Benznidazole tablets will be approved under the accelerated approval regulations 21 314.500 subpart H (b) (4). The applicant is required (b) (4) to verify and describe clinical benefit. The trial will be a prospective study with (b) (4) historical (b) (4) control (b) (4) to (b) (4) efficacy; safety (b) (4)

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

N/A

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

N/A

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

N/A

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

N/A

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

N/A

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☒ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
- ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☒ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸Error! Reference source not found.

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

--

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹⁰ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # 209570
PMR/PMC Set (####-#) 3247-2
Product Name: Benznidazole Tablets
Applicant Name: Chemo Research SL
ODE/Division: OAP/DAIP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a human absorption, distribution, metabolism, and excretion (ADME)/mass balance study to evaluate the routes and rates of benznidazole excretion, ascertain whether benznidazole has circulating drug metabolites, and if identified evaluate the routes and rates of excretion for benznidazole metabolites.

2. PMR/PMC Schedule Milestones^{11, 12}

Draft Protocol Submission:	10/2017
Final Protocol Submission:	11/2017
Study Completion:	04/2018
Final Report Submission:	08/2018

¹⁰ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

¹¹ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

¹² Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study¹³ or clinical trial¹⁴ in the text box below.

The information on the routes and rates of benznidazole excretion is not available and a human ADME/mass balance study was not submitted as part of the NDA. While this omission will not preclude approval, a postmarketing requirement to conduct the ADME study will evaluate the excretion routes and rates for benznidazole and its metabolites (if identified).

(b) (4)

(b) (4)

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

¹³ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

¹⁴ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS¹⁵ and Sentinel's postmarket ARIA¹⁶ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

¹⁵ FDA Adverse Event Reporting System (FAERS)

¹⁶ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☒ Other

Assessment of drug metabolites will not be included in FAERS data.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☒ Cannot identify exposure to the drug(s) of interest in the database.
- ☒ Serious risk (adverse event) of concern cannot be identified in the database.
- ☒ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☒ Important confounders or covariates are not available or well represented in the database.
- ☒ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☒ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

☒ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

An ADME/mass balance study will characterize the disposition of benznidazole and assess metabolite formation.

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

N/A

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☒ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements¹⁷Error! Reference source not found.

4. The PMR/PMC is clear, feasible, and appropriate¹⁸ because: *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

5. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

¹⁷ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

¹⁸ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.
6. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

APPEARS THIS WAY ON ORIGINAL

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹⁹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # NDA 209570
PMR/PMC Set (####-#) 3247-3
Product Name: TRADENAME (benznidazole)
Applicant Name: Chemo Research S.L.
ODE/Division: OAP/DAIP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct Study AB21206 entitled “Benznidazole – Fertility toxicity study by the oral route (twice daily gavage) in the male rat (Segment 1) followed by a 13-week treatment-free period”

2. PMR/PMC Schedule Milestones^{20, 21}

Draft Protocol Submission: NA
Final Protocol Submission: Submitted
Study/Trial Completion: Completed
Final Report Submission: 09/2017

¹⁹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

²⁰ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

²¹ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study²² or clinical trial²³ in the text box below.

(b) (4)

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

²² A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

²³ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS²⁴ and Sentinel's postmarket ARIA²⁵ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

²⁴ FDA Adverse Event Reporting System (FAERS)

²⁵ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

N/A

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

N/A

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

☒ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

An animal study is the generally accepted standard for assessment of a drugs protential to affect male fertility.

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

N/A

f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

An animal study is the generally accepted standard for assessment of a drugs potential to affect male fertility.

SECTION E: PMR/PMC Development Coordinator Statements²⁶Error! Reference source not found.

1. The PMR/PMC is clear, feasible, and appropriate²⁷ because: *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

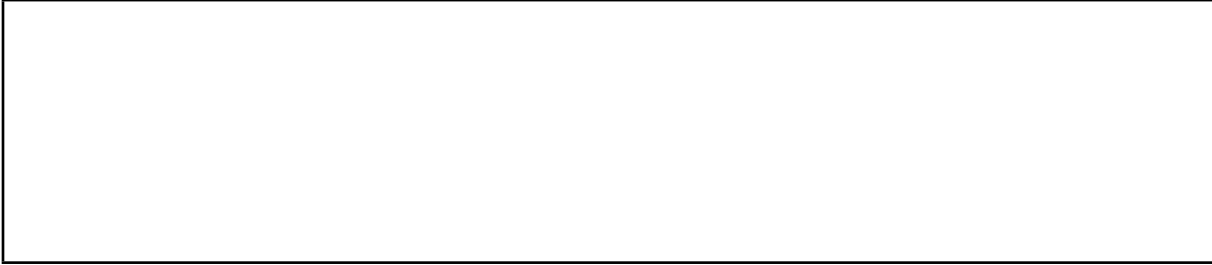
- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

²⁶ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

²⁷ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



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/s/

GREGORY F DIBERNARDO
08/28/2017

JOSEPH G TOERNER
08/28/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 24, 2017
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209570
Product Name and Strength:	Benznidazole tablets 12.5 mg tablet and 100 mg tablet
Applicant/Sponsor Name:	Chemo Research, S. L.
Submission Date:	August 24, 2017
OSE RCM #:	2016-3001-2
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and carton labeling for benznidazole tablets (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling reviews.^{a, b}

2 CONCLUSION

The revised container labels and carton labeling for benznidazole tablets are acceptable from a medication error perspective. We have no further recommendations at this time.

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

^a Kolejjan, S. Label and Labeling Review for Benznidazole tablet (NDA 209570). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 25. RCM No.: 2016-3001.

^b Kolejjan, S. Label and Labeling MEMORANDUM for Benznidazole tablet (NDA 209570). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 26. RCM No.: 2016-3001-1.

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/s/

SEVAN H KOLEJIAN
08/24/2017

OTTO L TOWNSEND
08/24/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 22, 2017

TO: Sumathi Nambiar, MD
Director
Division of Anti-Infective Products
Office of Antimicrobial Products

FROM: Ruben C. Ayala, Pharm.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDBE, OSIS

SUBJECT: Routine inspection of Bed Space for Short Stay at
Diagnostic and Consultative Centre Ascendent Ltd.,
Sofia, Bulgaria.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of bioavailability studies **LPR 1747-101** and **LPR 1747-102 (NDA 209570)** conducted at Bed Space for Short Stay at Diagnostic and Consultative Centre 'Ascendent' Ltd., Sofia, Bulgaria.

No significant objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I found the data from the audited studies reliable. Thus, I recommend that the data from studies **LPR 1747-101** and **LPR 1747-102** and other studies of similar design conducted at the site be accepted for further Agency review.

The recommendation is based on a summary of inspection findings provided by the ORA investigator and not on the final Establishment Inspection Report (EIR). The EIR is pending completion. This review may be amended if information in the final EIR affects the current recommendation.

Inspected Studies:

NDA 209570

Study Number: LPR 1747-101

Study Title: "A study to evaluate the food effect of a new formulation containing 100 mg benznidazole [Benznidazole 100 mg tablet (test) administered with and without high-fat breakfast]. A monocentric, open, randomized, single dose, two-period crossover trial in healthy volunteers"

Dates of conduct: 06/16/2015 - 06/30/2015

Study Number: LPR 1747-102

Study Title: "A study to evaluate the relative bioavailability of two formulations containing benznidazole (100 mg tablets and 12.5 mg tablets) administered intact or as a slurry under fasting conditions. A monocentric, open, randomized, single dose, three-period crossover trial in healthy volunteers"

Dates of conduct: 07/26/2016 - 08/17/2016

Clinical site: Bed Space for Short Term Stay at Diagnostic and Consultative Centre 'Ascendent' Ltd.,
47 Bacho Kiro Street,
Sofia, Bulgaria 1202

ORA investigator Sheri Oliver (OBIMO) inspected the clinical site Bed Space for Short Term Stay at Diagnostic and Consultative Centre 'Ascendent' Ltd., Sofia, Bulgaria from August 7-9, 2017.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, sponsor and monitor correspondence, test article accountability and storage, treatment randomization and allocation, adverse events, and case report forms. The inspection also covered compliance with slurry preparation and administration, blood sample collection times, and adherence to fed/fasting conditions.

Investigator Oliver uncovered documentation of delays (1-2 minutes) in sample collection times due to venipuncture issues. However, the site reported these events as protocol deviations in the study report. Therefore, the FDA is aware of the

findings. The minimal delay in collection times (1-2 minutes) is not likely to impact the study data.

At the conclusion of the inspection, investigator Oliver did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

Conclusion:

After reviewing the inspectional findings, I found the data from the audited studies to be reliable. Therefore, I recommend that the data from studies **LPR 1747-101** and **LPR 1747-102 (NDA 209570)** be accepted for further review.

In addition, studies of similar design conducted by the site before the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Ruben C. Ayala, Pharm.D.
Lead Pharmacologist

Final Classification:

Clinical Site

NAI - Bed Space for Short Term Stay at Diagnostic and
Consultative Centre 'Ascendent' Ltd.,
Sofia, Bulgaria
FEI#: 3009878236

cc:

OTS/OSIS/Kassim/Kadavil/Haidar/Turner-Rinehardt/Fenty-
Stewart/Nkah

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala

OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

OND/OAP/DAIP/Nambiar/Farley/Dibernardo

OCP/DCPIV/Lazor/Joshi

ORA/OBIMO/Oliver

Draft: RCA 8/22/2017

Edit: CB 8/22/2017

ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8810981ed>

OSIS File #: BE 7448

FACTS: 11731375

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/s/

RUBEN C AYALA
08/22/2017

CHARLES R BONAPACE
08/22/2017

Clinical Inspection Summary

Date	August 2, 2017
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Greg DiBernardo, Regulatory Project Manager Maria Allende, M.D., Medical Officer Tom Smith, M.D., Medical Team Leader Division of Anti-Infective Products (DAIP)
Application	NDA 209570
Applicant	Chemo Research, SL
Drug	Benznidazole (b) (4)
Original NDA	Yes
Review Priority	Priority
Proposed Indication	Treatment of Chagas disease
Consultation Date	May 2, 2017
CIS Goal Date	August 1, 2017
Action Goal Date	August 29, 2017
PDUFA Due Date	August 29, 2017

I. OVERALL ASSESSMENT OF FINDINGS

Published foreign studies (benznidazole for treating Chagas disease) were audited at good clinical practice (**GCP**) inspections of the applicant (Chemo Research, SL) and a clinical investigator (**CI**) site (Sosa-Estani). The CI site inspection revealed many GCP deficiency observations, typically (and apparently) recordkeeping deficiencies that included the following major study records no longer being available for review: (1) study protocol; (2) ethical committee oversight; (3) study medication disposition and accountability; and (4) subject informed consent. The findings at inspection of the applicant complemented those seen at the CI site inspection.

The study audited at the CI site was conducted over 20 years ago in collaboration with the World Health Organization (**WHO**), not under an IND and not intended to support a regulatory application. Given this regulatory context, a Form FDA 483 for GCP deficiencies was not issued at either inspection. The data from the CI site (Sosa-Estani) appear reliable as reported by the applicant in the NDA.

II. BACKGROUND

Chemo Research, SL seeks the approval of benznidazole (b) (4) for the treatment of Chagas disease (**CD**), the third most common parasitic disease in the world (after malaria and schistosomiasis). CD is caused by the protozoan parasite *Trypanosoma cruzi* when transmitted to humans by the triatomine bug (reduviid bed bug), by defecation on mucous membrane or skin bite with defecation. About 8 million people worldwide (mostly Latin America) live with CD-related (cardiac) morbidity, and over 10,000 die each year from CD. Currently there is no approved treatment for CD.

CD is considered rare in the United States but estimated prevalence is increasing with changing demographics and increasing public awareness. The effectiveness of the sponsor's study medication in treating CD (2014 Orphan Designation) as proposed in this NDA (Priority Review) is supported solely by foreign medical literature. The published studies were audited at GCP inspections of the sponsor and a CI site (Sosa-Estani) where the following key study was conducted.

Benznidazole Chagas Study

Efficacy of chemotherapy with benznidazole in children in indeterminate phase of Chagas disease. Estani S et al. The American Journal of Tropical Medicine and Hygiene 59(6):526-529, 1998

This double-blind randomized clinical trial was conducted between 1991 and 1995 in northwestern rural Argentina, at 14 localities considered endemic for *T. cruzi* and under continuous CD surveillance. Children assumed to be chronically (≥ 6 years) infected with *T. cruzi* were enrolled into the trial after screening and exclusion for any chronic health condition, acute or chronic infection (other than CD), unstable residence (social status), or lack of parental consent.

- 106 subjects were enrolled into the study, 55 for benznidazole and 51 for placebo. For each of the 14 localities (geographic strata), subjects were matched by age and the study treatment (benznidazole 5 mg/kg/day or matching placebo) were administered for 60 days by trained parents, teachers, or nurses.
- Efficacy evaluations were performed using serologic testing, immediately before and at 3, 6, 12, 18, 24 and 48 months after treatment initiation. An enzyme immunoassay (**EIA**) using *T. cruzi* flagellar antigen was used to assess parasitologic cure (**PC**). The serologic testing included EIA, indirect hemagglutinin assay (**IHA**), and indirect immunofluorescence assay (**IFA**).
- Safety evaluations were performed at Days 21 and 60, to include interim history including monitoring for adverse events (**AEs**), physical examination, electrocardiogram (**ECG**), hematology testing (including erythrocyte sedimentation rate), chemistry testing (including liver function tests, **LFTs**), and urinalysis.
- AEs were considered: (1) mild if study treatment was completed; (2) moderate if study treatment was suspended but without requiring special treatment; and (3) severe if study treatment was suspended and special treatment was required.

III. INSPECTION OUTCOMES

Establishment	Inspection Outcome*
Sergio Sosa-Estani, M.D. ⁽¹⁾ CeNDIE. Av Paseo Colón Buenos Aires, Argentina	July 7 – 10, 2017 NAI
Chemo Research, SL ⁽²⁾ Manuel Pombo Angulo 28 Madrid, Spain	July 14 – 20, 2017 NAI

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations

VAI = Voluntary Action Indicated, minor deviations from regulations

OAI = Official Action Indicated, major deviations from regulations

*For both inspections, the establishment inspection report (**EIR**) has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. An addendum to this clinical inspection summary (**CIS**) may be forwarded to the review division if new significant findings are discovered at EIR review; otherwise, OSI's written correspondence to the inspected entity (to be copied to review division) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

Sergio Sosa-Estani, M.D.

Benznidazole Chagas Study, Sosa-Estani Site: 3175 subjects were screened, 115 were enrolled, and 106 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 25 subjects.

The CI site inspection included verification that all subjects were: real (actually existed), given study treatment, evaluated for efficacy (serology), and monitored for AEs. The audit of subject case records included detailed review for 10 subjects (selected at random). The following NDA data listings were verified against on-site records:

- Listing A: subject disposition
- Listing B: randomization
- Listing F: adverse events
- Listing H: Quantitative and qualitative serology efficacy data
- Subject demographics

This foreign study was conducted over 20 years ago in collaboration with WHO, not under an IND and not intended to support a regulatory submission. A Form FDA 483 was deemed not applicable and not issued. The following GCP deficiency observations were verbally discussed in the context of the on-going NDA review:

- The following major study records were (apparently) no longer available for review:
 - Study protocol (lack of availability known prior to inspection, not included in NDA)
 - Ethical committee approval of study initiation and continuing oversight
 - Study medication disposition and accountability
 - Informed consent for all enrolled subjects
- For all (106) subjects completing study, the following were not available for review:
 - General medical records (one subject)
 - Serology records (3 subjects) or IFA serology data (15 subjects)
- Subject case records were incomplete or inaccurate (*see Section III, table footnote*):
 - Incomplete source serology records (5 subjects)
 - Source serology data discrepant with NDA data (9 subjects)
 - Missing baseline-interim-final clinical evaluations (3-10-7 subjects)
 - Missing baseline-interim-final urinalysis (5-15-22 subjects)
 - Missing final laboratory LFTs (17 subjects) or ECGs (16 subjects)

These deficiency observations appeared to reflect inadequate recordkeeping and unlikely to be significant to the study outcome as reported in the literature/NDA. All audited NDA data were adequately verifiable against on-site records.

Chemo Research, SL

This applicant inspection included a review of: (1) trial master files; (2) general study records, including correspondence with the publication authors; and (3) standard operating procedures for data management. Specifically:

- NDA data listings were verified against the original data collected from the publication authors (spreadsheets and original manuscripts).
- Written correspondence between the sponsor and the publication authors (including Sosa-Estani, De Andrade, and Viotti) were verified to be supportive of the NDA data.

All studies supporting this NDA were conducted over 20 years ago and subsequently published; none were sponsored by the applicant. Chemo Research contracted (b) (4) to collect and present in the NDA the original data for each study/publication. Records not relevant to NDA data verification and (apparently) no longer available for review included study protocols and documentation of ethical committee oversight, study medication accountability, and subject informed consent. Accordingly, no significant (applicable) deficiencies were identified and a Form FDA 483 was not issued. The data from the published studies appear reliable as reported in the NDA.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DAIP / Division Director / Sumathi Nambiar
DAIP / Medical Team Leader / Tom Smith
DAIP / Medical Officer / Maria Allende
DAIP / Regulatory Project Manager / Greg DiBernardo

OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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/s/

JONG HOON LEE
08/02/2017

JANICE K POHLMAN
08/03/2017

KASSA AYALEW
08/03/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 26, 2017
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209570
Product Name and Strength:	Benznidazole tablet 12.5 mg tablet and 100 mg tablet
Applicant/Sponsor Name:	Chemo Research, S. L.
Submission Date:	July 19, 2017
OSE RCM #:	2016-3001-1
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for benznidazole tablets (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for benznidazole tablets are unacceptable from a medication error perspective. Per 21 CFR 201.15(a)(6), the product strength should be prominent. As proposed, the product quantity statement is more prominent than the product strength statement on the container labels and carton labeling.

2.1 RECOMMENDATIONS FOR CHEMO RESEARCH, S. L.

We recommend the following be implemented prior to approval of this NDA:

1. The product strength statement should be more prominent than the product quantity statement on the container labels and carton labeling (see 21 CFR 201.15(a)(6)). Increase the strength statement's prominence on the container label and carton labeling. Also, increasing the prominence of the strength statement, can help address the risk of confusion between the 12.5 mg and 100 mg strengths. We have received postmarket medication errors reports describing product selection errors when a product's quantity (100) has been misinterpreted as the product's strength (100 mg) and vice versa. This medication error type has occurred when products are available in a quantity of 100 and available in multiple strengths including 100 mg.

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^a Koleyian, S. Label and Labeling Review for Benznidazole tablet (NDA 209570). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 25. RCM No.: 2016-3001.

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/s/

SEVAN H KOLEJIAN
07/26/2017

OTTO L TOWNSEND
07/26/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: July 26, 2016

To: Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): (b) (4) (benznidazole)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209570

Applicant: Chemo Research S.L.

1 INTRODUCTION

On December 29, 2016 Chemo Research S.L. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 209570 for (b) (4) (benznidazole) tablets, for oral use. The proposed indication for (b) (4) (benznidazole) tablets, for oral use is for the treatment of *American Trypanosomiasis* (Chagas disease), a disease caused by *Trypanosoma cruzi*.

On July 6, 2017 the Applicant submitted an Information Request-Response including Instructions for Use (IFU), in response to a June 14, 2017 request by the Division of Anti-Infective Products (DAIP) for the Applicant to develop written instructions to be distributed to patients on how to take the 100 mg functionally scored tablets.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by DAIP on July 14, 2017 for DMPP to review the Instructions for Use (IFU) for (b) (4) (benznidazole) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft (b) (4) (benznidazole) tablets, for oral use IFU received on July 6, 2017 and received by DMPP on July 14, 2017.
- Draft (b) (4) (benznidazole) tablets, for oral use Prescribing Information (PI) received on December 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on July 14, 2017.
- Approved ACTICLATE (doxycycline hyclate) tablets, for oral use comparator labeling dated April 26, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Arial font, size 11.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
07/26/2017

LASHAWN M GRIFFITHS
07/26/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: July 24, 2017

To: Gregory F. DiBernardo
Regulatory Health Project Manager
Division of Anti-Infective Products (DAIP)

From: Puja Shah, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 209570
TRADENAME (benznidazole) tablets, for oral use

As requested in DAIP's consult dated February 21, 2017, OPDP has reviewed the draft Package Insert (PI) and Carton and Container Labeling (CCL) for TRADENAME (benznidazole) tablets for oral use. OPDP's comments are based on the substantially complete version of the labeling titled "05.09.17 version draft-labeling-text-3apr2017.docx" which was accessed via <http://sharepoint.fda.gov/orgs/CDER-OAP-DAIP/Active%20Documents/05.09.17%20version%20draft-labeling-text-3apr2017.docx> on July 14, 2017.

Package Insert

Our comments on the draft PI are included directly on the attached copy of the labeling.

Carton and Container Labeling

OPDP reviewed the following proposed CCL accessed via <file:///CDSESUB1/evsprod/NDA209570/0001> on July 24, 2017, and does not have any comments at this time:

- Bottle-label-100mg.pdf
- Bottle-label-(b) (4) mg.pdf
- Box-label-100mg.pdf
- Box-label-(b) (4) mg.pdf

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
07/24/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: June 28, 2017 **Date Consulted:** May 18, 2017

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Maria Allende, MD, Clinical Reviewer,
Office of Antimicrobial Products (OAP),
Division of Anti-Infective Drug Products (DAIP)

Drug: (b) (4) (benznidazole)

NDA: NDA 209570

Indication: (b) (4) is an antiprotozoal indicated for the treatment of Chagas disease.

Applicant: Chemo Research, S.L.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's background package for NDA 209570 submitted as SD#1 on December 29, 2016.
- Applicant's revised label, submitted as SD#11 on April 7, 2017.

Consult Question: We would like your help in writing the PLLR sections, considering the preclinical toxicity findings and the paucity of human reproduction

and carcinogenetic toxicity reported. We are considering an indication for children (b) (4)

INTRODUCTION

On May 18, 2017, OAP/DAIP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of (b) (4) (benznidazole) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- Benznidazole (BNZ) is an antiprotozoal agent of the nitroimidazole group used to treat Chagas disease and is included in the WHO Essential Medicines List to treat Chagas disease. It has been adopted as a first choice in the treatment of Chagas disease in most endemic countries.^{1,2}
- In use since the early 1970s for the treatment of *Trypanosoma cruzi* infection, Chagas disease (CD).
- Not approved in the US.
- The original drug registration of benznidazole was performed by Roche in Brazil, Argentina, Bolivia, Uruguay, Peru, Nicaragua and Japan in the 1970s as Radanil®, Ragonil® or Rochagan®. In 2003, Roche decided to donate all commercial rights and the technology to manufacture benznidazole to the Brazilian government, Laboratorio Farmaceutico de Pernambuco (LAFEPE). Roche was the sole producer of benznidazole until the technology was transferred to LAFEPE.
- On December 29, 2016, Chemo Research, S.L. submitted a new NDA 209570 for (b) (4) (benznidazole).
- On April 7, 2017, the Applicant submitted revised labeling.

BACKGROUND

Benznidazole (BNZ) and Drug Characteristics³

- Proposed to be available as a tablet for oral use in the following doses: 100 mg BNZ (b) (4) scored tablets, 12.5 BNZ tablets [The 12.5 mg BNZ tablets may be (b) (4) made into a slurry for immediate administration for patients with (b) (4) body weight (i.e. pediatric patient)].
- The trypanocidal mechanism of action of BNZ is known to depend on a parasite type I nitroreductase (NTR). This enzyme is absent in mammalian cells, a difference that forms the basis for the drug selectivity. It catalyzes the 2-electron reduction of nitroheterocyclic compounds within the parasite, producing toxic metabolites without significant generation of superoxide⁴.

¹ Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. *Jama*. 2007; 298(18):2171-2181.

² Rassi A, Marin-Neto JA. Chagas disease. *The Lancet*. 2010; 375(9723):1388-1402.

³ (b) (4) (benznidazole) N 209570 proposed package insert

⁴ Wilkinson SR, Bot C, Kelly JM, Hall BS. Trypanocidal activity of nitroaromatic prodrugs: current treatments and future perspectives. *Curr Top Med Chem*. 2011; 11(16):2072-84.

- The dosage is determined by body weight (b) (4)
- The half-life of benznidazole is $\approx$ 12 hours.
- The molecular weight of benznidazole is $\approx$ 260 Daltons.
- The protein binding for benznidazole is $\approx$ 44%.
- Most common adverse reactions in clinical trials of (b) (4) (>10%) were headache, pruritis, nausea, abdominal pain, hypersensitivity, neutropenia, and rash.

Current State of the Labeling⁵

- No currently approved product in US or Canada.
- Current labeling for Rochagan (benznidazole) available in endemic countries in old format.
- There is no boxed warning for embryo-fetal toxicity.

Chagas Disease (CD) and Pregnancy

Chagas disease, or American trypanosomiasis, is a zoonosis caused by the parasite *Trypanosoma cruzi* (a flagellated protozoan parasite). World Health Organization (WHO) disease burden estimates place CD first among parasitic diseases in the Americas.⁶ Twelve million people are estimated to have CD, and 25,000 CD-related deaths occur each year in

⁵ Rochagan label (archival), accessed on Daily Med May 31, 2017.

⁶ WHO technical report, 2008

the world.⁷ On the basis of the size of the Latin American immigrant population and the estimates of *T. cruzi* prevalence in their home countries, it is estimated that 300,000 infected immigrants reside in the United States⁸. Infection is life-long in the absence of effective treatment. The most important consequence of *T. cruzi* infection is cardiomyopathy, which occurs in 20 to 30% of infected persons⁹.

Maternal infection can cause adverse effects during pregnancy relating to fetal growth and maturity, abortion, prematurity, increased neonatal mortality and transmission of Chagas Disease.^{10,11} Congenital transmission of *T. cruzi* is diagnosed when a neonate is born from an infected mother with positive serology or *T. cruzi* parasites circulating in the blood; when *T. cruzi* parasites are detected in the neonate at birth or shortly thereafter, or when *T. cruzi* antibodies not of maternal origin are detected after birth; and when transmission to the neonate by vectors or blood transfusion has been ruled out.⁷

Only two drugs, nifurtimox and benznidazole are currently available for the treatment of Chagas Disease, both with similar effectiveness and limitations^{12, 13}. Both drugs are associated with a high risk of toxicity in adults, especially dermatologic reactions¹². Benznidazole is the most commonly used drug in South America, due to availability issues¹².

Because safety of benznidazole in pregnancy has not been established, it is not recommended for use in treating pregnant women⁹. Prevalence of vertical transmission of *T. cruzi* infection from immunocompetent women to their fetus varies from 0.1% to 18% among regions¹⁴, and such transmission is strongly associated with the maternal blood-parasite load^{9,15}. However, patients co-infected with HIV exhibit higher levels of parasitemia and a higher congenital transmission rate than those who are not co-infected¹⁶. Overall, 60-90% of congenitally infected children are asymptomatic. A small percentage of infected children present with clinical conditions common to other congenital infections, including hepatosplenomegaly,

⁷ Corrêa VR *et al.* Uneventful benznidazole treatment of acute Chagas disease during pregnancy: a case report. *Rev Soc Bras Med Trop.* 2014. May-Jun; 47(3):397-400.

⁸ Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. *Clin Infect Dis* 2009; 49(5): e52-e54.

⁹ Rassi A Jr, Rassi A, Marcondes de Rezende J. American trypanosomiasis (Chagas disease). *Infect Dis Clin North Am* 2012; 26: 275-91.

¹⁰ Dao L. Otros casos de enfermedad de Chagas en el Estado Guárico (Venezuela): formas agudas y crónicas; observación sobre enfermedad de Chagas congénita. *Rev Policlín Caracas* 1949; 17:17-32.

¹¹ Carlier Y *et al.* Congenital Chagas disease: recommendations for diagnosis, treatment and control of newborns, siblings and pregnant women. *PLoS Negl Trop Dis.* 2011; 5:e1250.

¹² Jannin J, Villa L. An Overview of Chagas Disease Treatment. *Mem Inst Oswaldo Cruz.* 2007; 102 (Supl 1): 95-7.

¹³ Viotti R, Vigliano C. Etiological Treatment of Chronic Chagas Disease: Neglected “Evidence” by Evidence-Based Medicine. *Expert Rev Anti Infect Ther.* 2007; 5: 717-26.

¹⁴ Carlier Y, Truyens C. Maternal-fetal transmission of *Trypanosoma cruzi*, one hundred years of research. In: *American trypanosomiasis: Chagas disease.* London: Elsevier; 2010. p. 539–81.

¹⁵ Bern C *et al.* Congenital *Trypanosoma cruzi* transmission in Santa Cruz, Bolivia. *Clin Infect Dis.* 2009; 49:1667–74.

¹⁶ Scapellato PG *et al.* Mother-child transmission of Chagas disease: could coinfection with human immunodeficiency virus increase the risk? *Rev Soc Bras Med Trop.* 2009; 42:107–9.

sepsis, myocarditis, hepatitis, meningoencephalitis, edema, fever, anemia, and jaundice.^{17,18} Infected infants are presumed to carry the same 20–30% lifetime risk of cardiac or gastrointestinal disease as other infected individuals¹⁹.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”²⁰ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule²¹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

In an embryo-fetal study in (b) (4) rats, an oral dose of 150 mg/kg/day during organogenesis (days 6-17 of gestation) was associated with reduced fetal weights and smaller litter sizes. It also was associated with fetal malformations, (b) (4) eye abnormalities including microphthalmia and anophthalmia. (b) (4)

In an embryo-fetal study in pregnant rabbits, oral (gavage) administration of benznidazole during organogenesis (days 6 to 19 of gestation) at (b) (4) 25 mg/kg/day was associated with maternal (b) (4) including reduced weight gain and food consumption and abortions in 2/20 females (b) (4)

¹⁷ Carlier Y, Torrico F. Congenital infection with *Trypanosoma cruzi*: from mechanisms of transmission to strategies for diagnosis and control. *Rev Soc Bras Med Trop* 2003; 36: 767-771.

¹⁸ Rassi A *et al.* Busca retrospectiva da transmissão maternal da infecção chagásica em pacientes na fase crônica. *Rev Soc Bras Med Trop* 2004; 37:485-489.

¹⁹ Bern C *et al.* Acute and Congenital Chagas Disease. In: *Advances in Parasitology*, Volume 75. 2011. Elsevier Ltd.

²⁰ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

²¹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Benznidazole did not increase malformations and was not teratogenic in this study. The maternal NOAEL doses for maternal and fetal toxicity in this study were 7.5 and 25 mg/kg/day respectively which are equivalent to approximately 0.2 and 0.6 times the plasma AUC exposure associated with the maximum recommended dose in humans.

For further details, the reader is directed to the Nonclinical Review by James Wild, Ph.D.

Applicant's Review of Literature

The Applicant performed a literature search using the terms pregnancy and benznidazole in PubMed, Embase platform and LILACS database and identified nineteen publications. Of these, six were considered relevant and were submitted in full (the others were summarized or the abstract provided). Of the six, three case reports regarding benznidazole use in pregnancy were included (two in English, one in Spanish) and are summarized in Table 1 in the section of this review entitled "DPMH's Review of the Literature". One report of a screening program in Spain, which identified three pregnancies, is also included in Table #1.

DPMH's Review of the Literature

DPMH conducted a search of published literature in Embase using the search terms "benznidazole and pregnancy," "benznidazole and pregnant women," "benznidazole and pregnancy and birth defects," "benznidazole and pregnancy and congenital malformations," "benznidazole and pregnancy and stillbirth," "benznidazole and spontaneous abortion" and "benznidazole and pregnancy and miscarriage." No reports of adequate and well-controlled studies of benznidazole use in pregnant women were found. A few general articles discussing Chagas Disease with subsections on pregnancy were identified.

There is no reference to benznidazole in *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*²². Micromedex²³ has no information available on benznidazole. TERIS¹⁰ notes that the "Magnitude of teratogenic risk to child born after exposure during gestation is "undetermined" and that the "quality and quantity of data on which risk estimate is based is "none". TERIS does include a short summary of the case report by Correa²⁴ *et al.*, (2014) included in Table 1 below.

Table 1 summarizes what is known about the cases of pregnancy associated with Chagas Disease that are reported in the literature.

²² Briggs, GG, Freeman, RK, & Yaffe, SJ. (2015). *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

²³ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 5/31/17.

²⁴ Correa VR *et al.* Uneventful benznidazole treatment of acute Chagas disease during pregnancy: a case report. *Rev Soc Bras Med Trop* 47(3):397-400, 2014.

Table 1: Pregnancies Exposed to Benznidazole Reported in the Published Literature

Pregnancy # Author/Year/Country	Maternal Age	Diagnosis	Timing of Exposure/ Dose	Confounders	Outcome
#1 Bisio ²⁵ <i>et al</i> 2013 Argentina	33 years	HIV, Chagas reactivation with meningoencephalitis	Weeks 32-36, 5 mg/kg/day for 84 days	lamivudine, zidovudine, and nevirapine started at week 26 of pregnancy for HIV	Elective cesarean section at 36 weeks of 1700 gm female infant (low birth weight) with Apgars of 7/8 at 1+5 minutes, hospitalized for 32 days, negative for Chagas disease (at birth and one year) and HIV, no long term follow-up for infant reported
#2 Corrêa ²¹ <i>et al</i> 2014 Brazil	22 years	Chagas pericarditis and right bundle branch block (RBBB)	≈ first 2 weeks, 300mg/day X 4 weeks(wks), ↓200mg/day (for ↑ LFTs) X 3 months	None reported	Cesarean section at unreported gestational age (?term), negative for CD at 24 days and at 2-3 months, reported to have normal growth at that time
#3 Almuna ²⁶ <i>et al</i> (in Spanish) 1981 Chile	25 years	Chagas Disease	Week 32, 5mg/kg/day X 60 days	Given oral corticosteroids at week 34 for rash, h/o tuberculous pleurisy	Cesarean section at 36 weeks, delivery of a 2250 gm infant with Tetralogy of Fallot, Apgars of 8/8 at 1+5 minutes, no evidence of Chagas disease at birth
#4-6 Salas ²⁷ <i>et al</i> 2011 Spain	Not reported, 288 women screened, 3 positive	Chagas Disease	2 women treated with unknown dose and duration, one lost to follow-up	Not reported	No information reported except for the negative Chagas serology on the two infants of women from Bolivia

Source: Reviewer's Table

²⁵ Bisio M *et al*. Benznidazole Treatment of Chagasic Encephalitis in Pregnant Woman with AIDS. *Emerging Infectious Diseases*. 2013; 19, (9): 1490-1492.

²⁶ Almuna, R *et al*. Chagas disease and pregnancy. Review apropos of a clinical case. *Treatment. Revista chilena de obstetricia y ginecologia* 46.3 (1981): 107.

²⁷ Salas J *et al*. Chagas screening in pregnant women from Latin America: Experience in western Almeria. *Tropical Medicine and International Health*. 2011; 16 Suppl.1: 288.

Summary

Very limited human pregnancy outcome data (three cases with information on infant outcomes) were found in the published literature for benznidazole. Two of the three exposures were in the third trimester, and therefore, are uninformative with regards to potential teratogenicity. The third case was similarly uninformative due to very early exposure (within the first 2 weeks after conception, therefore likely before implantation). The findings in animal studies demonstrated increased fetal loss and eye anomalies at doses under the maximum human doses. Since there is evidence of fetal risk based on animal studies, a signal for mutagenicity and limited available data in humans, DPMH agrees with the Applicant and recommends that benznidazole not be used routinely during pregnancy (ie individual cases where maternal or fetal mortality or significant morbidity is threatened may be the exceptions). In addition, DPMH recommends adding a Warning and Precaution for embryo-fetal toxicity to the labeling for benznidazole.

Though information in the published literature is limited, there are reported increases in adverse pregnancy outcomes associated with Chagas Disease^{10, 11}. These publications are summarized in Table 2 below and were used as a basis to craft the clinical considerations subsection for section 8.1 which will read as follows:

Disease-associated maternal and/or embryo/fetal risk

Published data from case-control and observational studies on chronic Chagas Disease during pregnancy are inconsistent in their findings. Some studies showed an increased risk of pregnancy loss, prematurity and neonatal mortality in pregnant women who have chronic Chagas Disease while other studies did not demonstrate these findings. Chronic Chagas Disease is usually not life-threatening. Since pregnancy findings are inconsistent, treatment of chronic Chagas Disease during pregnancy is not recommended due to risk of embryofetal toxicity from (b) (4).

Acute symptomatic Chagas Disease is rare in pregnant women; however, symptoms may be serious or life-threatening. There have been reports of pregnant women with life-threatening symptoms associated with acute Chagas Disease who were treated with benznidazole. If a pregnant women presents with acute symptomatic Chagas Disease, the risks versus benefits of (b) (4) treatment to the mother and the fetus should be evaluated on a case-by-case basis.

Table 2: Publications to Support Clinical Considerations For (b) (4)

Author/ Year/ Country	Total # of patients	Diagnostic test for Chagas	Age Range (years)	Conclusions/ Outcomes	Comments
Torrico 2004 Bolivia	Cohort A ² =1606 Cohort B ³ =3879 Within B: 100/762 M+B- pairs in study, 99/3070 M-B- pairs in study	A, M-B- ⁴ : 1162 A, M+B- ⁵ : 422 A, M+B+ ⁶ : 22 B, M-B- ⁴ : 99 B, M+B- ⁵ : 100 B, M+B+ ⁶ : 47 All with IHAT		Mothers of positive babies had 3-4 fold [↑] in PROM ⁷ , Apgars, birth weights and lengths, gestational ages and head circumference [↓] in positive babies, Mortality was significantly [↑] in M+B+ babies in both cohorts, 5-6% transmission of Chagas in both cohorts	Maternal T.Cruzi infection affects intrauterine growth and maturity of congenitally infected infants, but not of non-infected fetuses.
Schenone 1985 Chile	506 urban + rural women	266 IHAT ²⁸ + 240 IHAT -	10-40	No difference in mean weight of infants at birth	
Bittencourt 1984 ?Brazil				Compared the frequency of prematurity, abortion, stillbirths and neonatal deaths in chagasic and non chagasic mothers and in a group of chagasic women who transmitted the infection-only difference is [↑] neonatal deaths in infected infants	
Hernandez- Matheson	604 patients	302 GMCFT ²⁹ + 302 GMCFT-		1.8 Fold [↑] in pregnancy loss (SAB ³⁰ , stillbirths, neonatal death in the first week of life) after adjustment for	No difference in rate of prematurity

²between 1992-1994, 1606 patients screened ³between 1999-2001, 3879 patients screened ⁴M-B- : Mother and baby negative for Chagas ⁵M+B-: Mother positive and baby negative for Chagas ⁶ M+B+: Mother and baby positive for Chagas

⁷PROM= Premature rupture of membranes

²⁸ Indirect hemagglutination test

²⁹ Guerreiro and Machado complement fixation test

³⁰ SAB=spontaneous abortion

Author/ Year/ Country	Total # of patients	Diagnostic test for Chagas	Age Range (years)	Conclusions/ Outcomes	Comments
1983 Argentina				maternal age and birth order, ↑ in polyhydramnios and leg varicosities	
De Castilho 1976 ?Brazil	249 low birth weight (<2500 gm) live births	Indirect IF ³¹ test	Mean age≈ 26	No association between Chagas disease and prematurity after matching to controls of same sex, birth order and maternal age	Excluded known causes of premature birth such as placenta previa, eclampsia, HTN
Oliveira 1966 ?Brazil	200	67 GMCFT ³² + 133 GMCFT-		No difference in rate of spontaneous abortion	

Source: Reviewer's Table

³¹ IF=immunofluorescence

³² Guerreiro and Machado complement fixation test

Lactation

Nonclinical Experience

There is no data available from animal studies regarding benznidazole's presence in milk or effects on lactation.

Applicant's Review of Literature

The Applicant performed a literature search using the terms lactation and benznidazole in PubMed, Embase platform and LILACS database and identified nine publications. Those relevant to this review are included below in the discussion in the section of this review entitled "DPMH's Review of the Literature".

DPMH Review of the Literature

DPMH conducted a search of *Medications and Mother's Milk*³³, the Drugs and Lactation Database (LactMed),³⁴ Micromedex³⁵, and of published literature in Embase using the search terms "benznidazole and lactation" and "benznidazole and breastfeeding." No reports of adequate and well-controlled studies of benznidazole use in lactating women were found. The following publications were identified as relevant and are summarized below.

- Marson M³⁶ *et al* (2013) reported on development of an "accurate, sufficiently sensitive" method for the quantification of benznidazole in human milk. They obtained 17 breast milk samples at unspecified times from 10 women being treated for Chagas Disease with benznidazole 5-10 mg/kg/day. Breast milk concentration varied from undetectable (0.3 mg/L) and 9.8 mg/L, with a mean of 4.1 mg/L. The authors calculated that a fully breast fed infant would receive between 0.6-1.5 mg/kg daily dose
- Garcia-Bournissen,³⁷ *et al* reported on twelve lactating women treated for 30 days with benznidazole (BNZ) at an average dose of 5.65 mg/kg/day administered twice daily. The mean maternal age was 28.5 years. Median breast milk concentration was 3.8 mg/L (range 0.3-5.9) and 6.26 mg/L (range 0.3-12.6) in plasma. The median milk: plasma ratio was 0.52 (range 0.3-2.79). The median relative infant dose (assuming a daily milk intake of 150 ml/kg/day) was 12.3% of the maternal dose per

³³ Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

³⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

³⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 5/31/17.

³⁶ Marson M *et al*. A Simple and Efficient HPLC Method for Benznidazole Dosage in Human Breast Milk. *Ther Drug Monit*. 2013; 35:522–526.

³⁷ Garcia-Bournissen F *et al*. Limited Infant Exposure to Benznidazole through Breast Milk during Maternal Treatment for Chagas Disease. *Arch Dis Child*. 2015; 100: 90-94.

kg (range 5.5-17%). No adverse effects were noted in the breastfed infants. The authors called this amount of milk transference “limited” and stated that in their opinion maternal BNZ treatment of Chagas disease was unlikely to present a risk to the breastfed infant.

- Padro JM *et al.*³⁸ reported on four women with Chagas disease who were treated with benznidazole 5 to 10 mg/kg daily in 2 divided doses and provided breastmilk samples for analysis after 4 to 10 days of therapy. The timing of the sample with respect to doses was not reported. Breastmilk concentrations of benznidazole ranged from nonquantifiable (<0.88 mg/L) to 7.1 mg/L.

Benznidazole is not referenced in *Medications and Mother’s Milk*²³ or MicroMedex¹⁰. LactMed⁹ notes the following in the “Summary of Use during Lactation”

Benznidazole is excreted into milk in dosages much lower than the treatment dosage for infants. Because of the low levels of benznidazole in breastmilk and safety when given directly to infants, its use is acceptable in nursing mothers.

Summary

There are data on the presence of benznidazole in human milk. A calculated relative infant dose of 12.3% was reported from a study of 12 lactating women³¹. Though LactMed finds this level acceptable and notes that it is much lower than doses given directly to infected infants, DPMH has concerns that the risk/benefit calculus for a non-infected infant in the United States (where alternatives to breast feeding are readily available) is less certain given the mutagenicity and carcinogenicity found in nonclinical models treated with doses of the product comparable to doses used for infected patients. This issue was discussed with the clinical team, the pharmacology/toxicology team and the clinical pharmacologist from DAIP and consensus was reached that “Breastfeeding is not recommended” during use of benznidazole.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

In a pre- postnatal study in rats, first generation (F1) pups born to dams administered 15, 50, or 75 mg/kg/day benznidazole demonstrated normal pre-weaning behavior, physical and functional development, neurological findings, and reproductive parameters. However, cesarean section data for first generation (F1) females in the high-dose group included significantly higher pre-implantation loss and significantly lower mean values for corpora lutea counts, number of implantations, and number of live embryos. Also small testes and/or epididymides were observed in 1/20 and 2/20 F1 males in the mid- and high-dose groups respectively, and two of the affected animals failed to mate or induce pregnancy. However, the mean values for mating performance, fertility index, testes weight, testes and

³⁸Padro JM *et al.* Development of an ionic-liquid-based dispersive liquid-liquid microextraction method for the determination of antichagasic drugs in human breast milk. Optimization by central composite design. J Sep Sci. 2015; 38:1591-600.

epididymides sperm counts, and epididymal sperm motility and progression were not altered in any of the F1 males in benznidazole treatment groups. The NOAEL value was considered to be 50 mg/kg/day which is equivalent to approximately 0.6 times the maximum recommended dose in humans based on whole body surface area comparisons.

The carcinogenicity of benznidazole was evaluated in mice and in rabbits (Teixeira, 1990a, 1990b, 1994) treated for up to 60 consecutive days by intraperitoneal injection at doses of 8 mg/kg/day. Treatment-related lymphomas were induced in both species. Genotoxicity of benznidazole has been shown to occur *in vitro* in several bacterial species and mammalian cell systems and *in vivo* in mammals including humans.

For further details, the reader is directed to the Nonclinical Review by James Wild, Ph.D.

Applicant's Review of Literature

The Applicant performed a literature search using the terms fertility and benznidazole in PubMed, Embase platform and LILACS database and identified four publications. The Applicant did not find these relevant to labeling and the articles were not provided.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding benznidazole and its effects on fertility and found several nonclinical articles which will not be discussed further in this review as they are not to be included in labeling. Articles regarding the toxicity, mutagenicity and potential carcinogenicity of benznidazole were reviewed, and in addition to the animal findings, contributed to concerns about the use of this product in pregnancy and lactation.

Summary

There are no human data available on the effect of benznidazole on fertility. Based on animal fertility studies, benznidazole may impair fertility in male patients. Therefore, section 8.3 will also contain a section describing the potential for benznidazole to impair male fertility. Based on the animal findings and the Warning and Precaution regarding embryo-fetal toxicity, recommendations for pregnancy testing and contraception will be added to section 8.3.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for (b) (4) (benznidazole) labeling:

- **Pregnancy, Section 8.1**

- The “Pregnancy” section of (b) (4) (benznidazole) labeling was structured in the PLLR format to include the “Risk Summary”, “Clinical Considerations” and “Data” sections.³⁹
- **Lactation, Section 8.2**
 - The “Lactation” section of (b) (4) (benznidazole) labeling was formatted in the PLLR format to include the “Risk Summary” section.⁴⁰
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” section of (b) (4) (benznidazole) labeling was formatted in the PLLR format to include the “Pregnancy testing”, “Contraception” and “Infertility” sections.⁴¹

LABELING RECOMMENDATIONS

DPMH revised the HPI and sections 5.*, 8.1, 8.2 and 8.3 and 17 of (b) (4) (benznidazole) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DAIP on 6/8/17 and 6/20/17. DPMH refers to the final NDA action for final labeling.

DPMH Proposed (b) (4) (benznidazole) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

Embryo-Fetal Toxicity: Can cause fetal harm. Pregnancy testing is recommended for females of reproductive potential. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.x, 8.1, 8.3)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Breastfeeding not recommended. (8.2)

FULL PRESCRIBING INFORMATION

2 Dosage and Administration

- | Obtain a pregnancy test prior to (b) (4) therapy.

5.x Embryo-Fetal Toxicity

³⁹ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

⁴⁰ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

⁴¹ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection C-8.3 Females and Males of Reproductive Potential.

Based on findings from animal studies, (b) (4) can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, (b) (4) the maximum recommended human dose) during organogenesis was associated with fetal malformations, (b) (4) microphthalmia and anophthalmia, reduced (b) (4) weights and smaller litter sizes. Advise pregnant women of the potential risk to a fetus. Pregnancy testing is recommended for females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with (b) (4) and for 5 days after the last dose [see *Use in Specific Populations* (8.1), (8.3) and *Clinical Pharmacology* (12. (b) (4))].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, (b) (4) cause fetal harm when administered to a pregnant woman. Published postmarketing reports on benznidazole use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. There are risks to the fetus associated with Chagas Disease (see *Clinical Considerations*). In animal reproduction studies, benznidazole administered orally to pregnant rats and rabbits during organogenesis was associated with fetal malformations at doses approximately 1-3 times the maximum recommended human dose (MRHD) in rats (anasarca, anophthalmia, and/or microphthalmia) and doses approximately 0.3-1.3 times the MRHD in rabbits (ventricular septal defect). (see *Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Published data from case-control and observational studies on chronic Chagas Disease during pregnancy are inconsistent in their findings. Some studies showed an increased risk of pregnancy loss, prematurity and neonatal mortality in pregnant women who have chronic Chagas Disease while other studies did not demonstrate these findings. Chronic Chagas Disease is usually not life-threatening. Since pregnancy findings are inconsistent, treatment of chronic Chagas Disease during pregnancy is not recommended due to risk of embryofetal toxicity from (b) (4).

Acute symptomatic Chagas Disease is rare in pregnant women; however, symptoms may be serious or life-threatening. There have been reports of pregnant women with life-threatening symptoms associated with acute Chagas Disease who were treated with benznidazole. If a pregnant woman presents with acute symptomatic Chagas Disease, the risks versus benefits

of (b) (4) treatment to the mother and the fetus should be evaluated on a case-by-case basis.

Data

Animal Data

In an embryo-fetal toxicity study in pregnant rats, an oral dose of benznidazole of 150 mg/kg/day during organogenesis (days 6-17 of gestation) was associated with maternal weight loss, reduced fetal weights, and smaller litter sizes. Benznidazole was also associated with fetal malformations including anasarca at a dose of 50 mg/kg/day and anasarca and eye abnormalities (anophthalmia and microphthalmia) at a dose of 150 mg/kg/day (approximately equivalent to 1 and 3 times the maximum recommended human dose based on whole body surface area comparisons). The NOAEL dose for maternal toxicity in this study, 50 mg/kg/day, is approximately equal to the maximum recommended dose in humans based on body surface area comparisons. The NOAEL dose for fetal toxicity was 15 mg/kg/day which is approximately equivalent to 0.3 times the maximum recommended dose in humans based on whole body surface area comparisons.

In an embryo-fetal study in pregnant rabbits, oral (gavage) administration of benznidazole during organogenesis (days 6 to 19 of gestation) at a dose of 25 mg/kg/day was associated with maternal toxicity including reduced weight gain and food consumption and abortions in 2/20 females in this group. Benznidazole was also associated with fetal abnormalities including ventricular septal defect at a doses of 7.5 and 25 mg/kg/day (approximately equivalent to 0.3 and 1.3 times the maximum recommended human dose based on whole body surface area comparisons). The NOAEL values for maternal and fetal toxicity in this study were 7.5 and 2.5 mg/kg/day respectively, which are equivalent to approximately 0.3 and 0.1 times the maximum recommended dose in humans based on body surface area comparisons.

In a pre- postnatal study in rats, first generation (F1) pups born to dams administered 15, 50, and 75 mg/kg/day benznidazole demonstrated normal pre-weaning behavior, physical and functional development, neurological findings, and reproductive parameters. However, cesarean section data for first generation (F1) females in the high-dose group included significantly higher pre-implantation loss and significantly lower mean values for corpora lutea counts, number of implantations, and number of live embryos. Also small testes and/or epididymides were observed in 1/20 and 2/20 first generation males in the mid- and high-dose groups respectively, and two of the affected animals failed to mate or induce pregnancy. However, the mean values for mating performance, fertility index, testes weight, testes and epididymides sperm counts, and epididymal sperm motility and progression were not altered in any of the F1 males in benznidazole treatment groups. The number of live second generation (F2) fetuses born to F1 dams was reduced in the high-dose group. The NOAEL value was considered to be 50 mg/kg/day which is approximately equal to the maximum recommended dose in humans based on body surface area comparisons.

8.2 Lactation

Risk Summary

Limited published literature based on breast milk sampling reports that benznidazole is present in human milk at infant doses of 5.5 to 17% of the maternal weight-adjusted dosage

and a milk/plasma ratio ranging between 0.3-2.79. There are no reports of adverse effects on the breastfed infant and no information on the effects of benznidazole on milk production. Because of the potential for serious adverse reactions, (b) (4), advise patients that breastfeeding is not recommended during treatment with (b) (4).

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential.

Contraception

Females

(b) (4) can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations* (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with (b) (4) and for 5 days after the final dose.

Infertility

Males

Based on findings in (b) (4) may impair fertility in males of reproductive potential. It is not known whether effects on fertility are reversible [see *Nonclinical Toxicology* (13.1)].

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (b) (4)

- **Embryo-Fetal Toxicity**

Advise pregnant women and females of reproductive potential that exposure during pregnancy can result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.5) and *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception while taking (b) (4) and for 5 days after the last dose [see *Use in Specific Populations* (8.3)].

- **Lactation**

Advise women not to breastfeed during treatment with (b) (4) [see *Use in Specific Populations* (8.2)].

- **Infertility**

Advise males of reproductive potential that (b) (4) may impair fertility [see *Use in Specific Populations* (8.3) and *Nonclinical Toxicology* (13.1)]

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/s/

JANE E LIEDTKA
06/28/2017

MIRIAM C DINATALE
06/28/2017

LYNNE P YAO
07/05/2017

From: Noel Gerald, Ph.D., Kathleen Whitaker, Ph.D., and David Goodwin, Ph.D.,
Division of Microbiology Devices, OIR, CDRH

To: Maria Allende, MD, and Shukal Bala, Ph.D., Division of Anti-Infective
Products, CDER

Date: June 6, 2017

Consult #: NDA 209570
Product: (b) (4) (benznidazole) tablet 100mg & 12.5mg
Sponsor: Chemo Research, S.L.

Through: Uwe Scherf, M.Sc., Ph.D., Director, Division of Microbiology Devices, OIR,
CDRH

Background:

CDER/DAIP requested CDRH/OIR/DMD input on the validation of Chagas disease in vitro diagnostics that have been proposed for various uses to demonstrate the efficacy of benznidazole. Benznidazole is a new molecular entity (NME) intended for the treatment of Chagas disease. This drug is used in treatment of Chagas disease in other parts of the world and the sponsor is seeking FDA approval.

Consult Review Comments to CDER:

The following review comments are provided for internal discussion and consideration.

Positive results from at least two serological assays using *T. cruzi* antigens have been considered evidence of exposure to *T. cruzi*. A variety of different assay platforms, antigen preparations, and output measures have been used for these purposes. Due to the challenges of directly detecting the organism during infection, different serological assay results have also been considered as evidence of treatment efficacy in the field. Potential difficulties with this approach have been discussed in the clinical literature, and are common to serological assays that are used for other infectious diseases (e.g., persistence of some antibodies after infection resolution, slow changes in antibody response, potential cross reactivity with other infections, etc.).

Among the preclinical and clinical evidence presented in the NDA, the applicant presented information to support the use of *T. cruzi* serological assay results as surrogate markers for parasite reduction and potentially clearance (sterile cure). It is proposed that as surrogate markers of parasite reduction, these serological results could also be used as surrogate markers to predict clinical disease progression (or lack thereof) in *T. cruzi* infected patient (b) (4)

Overall recommendation:

The regulatory decision to approve or not approve benznidazole for the proposed indications should rely foremost on the results of clinical outcome measures as primary endpoints in the context of known risks. There is uncertainty about the performance characteristics of the assays highlighted in the NDA, and there is uncertainty about the predictive power of serological results to reliably discriminate which subjects will go on to receive clinical benefit. Thus, while the applicant has provided evidence of an overall trend of a reduced serological assay result signal in the benznidazole arms when compared to the placebo treatment arms from two small randomized controlled trials, it is not clear that a precise estimate of treatment effect could be calculated from these serological results alone. Our recommendation is that serological results be considered supportive information (b) (4)

Additional details are discussed below, including the recommendation that the ELISA assays should be interpreted as qualitative assays.

Serological assays described in the two RCTs

Specific review comments are provided for the serological assays described in two randomized placebo controlled trials conducted in 1996 and 1998. The submission discussed a variety of enzyme linked immunoassays (ELISA), indirect immunofluorescence assays (IFA), and indirect hemagglutination assays (IHA). The assays were considered to be either conventional or non-conventional serological assays as described below. The assays are listed in Tables 1 and 2.

Table 1. Serological assays discussed in De Andrade *et al.* Lancet (1996) 348:1407

Assay	Lit. Reference	Antigen Used	Assay Format	Assay cut-offs (ref)	Control/ Calibrator	Precision
ELISA (Conventional)	Voller 1975 Andrade 1992	Whole cell lysate from cultured parasites	Colorimetric ELISA. Read with a spectrophotometer.	Pos > 0.4 OD ¹ Pos >= 1.2 Index ²	?	?
IFA (Conventional)	Andrade 1992	Whole cultured parasites on slides	Indirect immunofluorescence. Read visually by microscopy.	Pos >= 1:20 titer ³ Pos >= 1:40 titer ²	?	?
IHA (Conventional)	Andrade 1992	Whole cell lysate from cultured parasites	Indirect hemagglutination. Read visually, macroscopic.	Pos >= 1:10 titer ³ Pos >= 1:16 titer ²	?	?
AT ELISA[†] (Non-conventional.)	Almeida 1994	Purified F2/3 antigens from cultured trypomastigotes	Chemiluminescent ELISA. Read by exposed film, then by densitometry in a spectrophotometer	Cut-off = (10 x mean negative ctrl) - (mean background ctrl). Pos > 1.0 Index ²	Neg ctrl Bckgrnd ctrl	?

¹ Voller, *et al.* Lancet (1975) i:426

² De Andrade, *et al.* Lancet (1996) 348:1407

³ Andrade, *et al.* Bull. World Health Org. (1992) 70:625

[†] Proposed that assay results determine treatment efficacy outcome.

Table 2. Serological assays discussed in Sosa-Estani *et al.* Am.J.Trop.Med.Hyg. (1998) 59:526

Assay	Lit. Reference	Antigen Used	Assay Format	Assay cut-offs (ref)	Control/ Calibrator	Precision
ELISA (Conventional)	Voller 1975	Whole cell lysate from cultured parasites	Colorimetric ELISA. Read with a spectrophotometer.	Pos > 0.4 OD ¹ Pos >= 0.205 OD ²	?	?
IFA (Conventional)	Alvarez 1968	Whole cultured parasites on slides	Indirect immunofluorescence. Read visually by microscopy.	Pos >= 1:32 titer ²	Pos ctrl Neg ctrl Fluor ctrl	?
IHA (Conventional)	Cerisola 1971	Whole cell lysate from cultured parasites	Indirect hemagglutination. Read visually, macroscopic.	Pos >= 1:32 titer ²	Neg ctrl	?
F29 ELISA[†] (Non-conventional.)	Porcel 1996 [#]	Recombinant F29 antigen	Colorimetric ELISA. Read with a spectrophotometer.	Pos >= 0.174 OD ²	Neg ctrl Bckgd ctrl	?

¹ Voller, *et al.* Lancet (1975) i:426

² Sosa-Estani 1998 – Cut-offs are inferred from line data. Cut-offs were not reported in this publication.

[†] Proposed that assay results determine treatment efficacy outcome.

[#] The cited reference describes the target antigen gene, not the specific assay in question.

Detecting decreases in anti-parasite antibodies over time

The decrease in anti-parasite antibodies over time (with or without full conversion to seronegative status) has been proposed as surrogate evidence for the reduction of parasite burden, and thus a surrogate endpoint for treatment efficacy. The applicant has described antibody reduction as changes in IFA/IHA titer results, and also as changes in ELISA numerical results. Both types of measurements are discussed below.

Decreases in IFA/IHA titer results – general comments

1. IFA and IHA are conventional assays that use whole parasite and whole parasite lysates, respectively, and so these assays detect a broad mixture of antibodies to many different *T. cruzi* antigens.
2. Defining the term titer in relation to IFA/IHA.

Titer results are produced when qualitative assays such as IFA/IHA are performed on serially diluted samples. Each dilution is tested individually, and the most dilute sample that is positive by the assay is reported as the titer (e.g., 1:16 or 1:256). Samples with high antibody concentration require many serial dilutions before a negative result is produced.

3. Titer results are relative, not absolute values.

As in other disease examples (e.g., syphilis nontreponemal antibodies), it is understood that titers cannot be compared between different assay platforms, nor are they necessarily comparable for results of the same assay performed at different labs.

4. Titer change and clinical relevance.

It is not clear what would be considered a clinically relevant antibody titer change for *T.*

cruzi infection. Ideally, there would be an established consensus in the field (e.g., a four-fold or greater change in syphilis nontreponemal assay titers is considered significant). We are not aware of a consensus of clinically relevant levels of *T. cruzi* antibodies. Different measures are described in the *T. cruzi* literature depending on the setting (e.g., two or three-fold changes, titer changes after conversion to geometric mean, etc.)

5. Assay reproducibility.

Under ideal circumstances, the reproducibility (precision) of the assays should also be taken into consideration when evaluating changes in antibody titer. For example, if an assay titer result can vary plus or minus one doubling dilution due to intrinsic technical/procedural effects, then a two-fold titer change would not be considered significant in this assay. It is not clear what the within-assay or between-assay variability was for the IFA and IHA assays used in the RCTs.

Differences noted between IFA and IHA results in the two RCTs

6. The IFA and IHA assays reported different titer result trends in each RCT.

In the Sosa-Estani trial, IHA titers were generally higher than IFA titers for the same samples at baseline. In contrast, in the De Andrade trial, IFA titers were generally higher than IHA titers for the same samples at baseline. The reasons for this discrepancy are not clear, but could be attributable to differences in reagent preparations, technician subjectivity for manually read assays, quality control measures, or differences in lab environments (e.g., humidity can affect IHA readings).

7. In each trial, the assay that tended to report higher titers at baseline showed the more dramatic decrease in titer values after drug treatment for that trial.

This can be crudely illustrated by assuming for the sake of argument that a four-fold or more change in titer is significant (allowing for an inherent assay variability of plus or minus one doubling dilution). In the De Andrade trial, IFA reported the larger number of patients with a four-fold or more titer change; in the Sosa-Estani trial, IHA reported the larger number of patients with four-fold changes. See Tables 3 and 4.

While an overall trend can be described of reduced antibody titers following treatment, the degree of observed antibody reduction is highly dependent on the assay used, the trial, and the criteria used to define a significant decrease.

Table 3. De Andrade– IHA/IFA Change in Titer Results – Follow-up at Month 36

		4-fold or more Decrease	± 2-fold Change, or No Change	4-fold or more Increase
IFA	BNZ	79.3% (46/58)	20.7% (12/58)	0
	Placebo	22.2% (12/54)	70.4% (38/54)	7.4% (4/54)
IHA	BNZ	62.1% (36/58)	36.2% (21/58)	1.7% (1/58)
	Placebo	16.7% (9/54)	72.2% (39/54)	11.1% (6/54)

Table 4. Sosa-Estani– IHA/IFA Change in Titer results – Follow-up at Month 48

		4-fold or more Decrease	± 2-fold Change, or No Change	4-fold or more Increase
IFA	BNZ	29.2% (14/48)	64.6% (31/48)	6.25% (3/48)
	Placebo	11.4% (5/44)	65.9% (29/54)	22.7% (10/44)
IHA	BNZ	70.8% (34/48)	29.2% (14/48)	0
	Placebo	25% (11/44)	70.5% (31/44)	4.5% (2/44)

Interpreting decreases in individual ELISA numerical results.

8. ELISAs produce an underlying numerical output value from a sample reading. For most colorimetric ELISAs that are read in a spectrophotometer, this value is the raw optical density (OD) value. Other values such as relative light units (RLUs) can be used for ELISAs that have a chemiluminescent format.
9. ELISA results can also be reported as index signal-to-cutoff (S/CO) values in which the raw output value for each sample is divided by an assay cut-off value.

For example: 0.180 OD value / 0.150 OD cut-off value = 1.2 Index S/CO value.

10. Usefulness of a calibrator reagents and controls for ELISAs. Ideally, an assay manufacturer/developer establishes the assay cut-off value (positive/negative determination) by providing a separate control or calibrator reagent that is included with each test run. A calibrator can reduce assay variability from run-to-run, lot-to-lot of reagents, etc. by serving as a unified standard for establishing the cut-off.

Alternatively, the assay cut-off can be defined using parameters from each assay run.
For example:

Cut-off value = 10 X the mean value of the negative control sample result – the mean value of the background control result

This approach may allow greater assay variability between runs or between reagent preparations over time.

As an illustration of the range of assay variability that is possible for ELISAs, a subset of precision results from two FDA-cleared Chagas disease serology ELISA package inserts are shown in Table 5. The largest variability (%CV) that was observed run-to-run was 5.1% in one test and 15.8% in the other.

Table 5. Examples of assay variability reported for two ELISAs

510(k) #	K072732	K023889
Test name	ORTHO <i>T. cruzi</i> ELISA	Chagatest ELISA recombinante V3
Capture antigen	Whole cell lysate	Recombinant antigens
Cut-off method	Calibrator	Mean NC + 0.30 OD
Test output	S/CO	OD
# of precision replicates tested	540	60
Largest reported %CV (SD/mean)	5.1%	15.8%

11. We recommend that changes in individual ELISA numerical results not be used to infer a quantitative assessment of antibody decrease. The qualitative result (positive/negative) is the more appropriate output interpretation for single-read ELISAs.
 - a. The ELISAs used in the two RCTs provide a single qualitative result for each sample measurement. It is not appropriate to assume that qualitative ELISA results can be interpreted as absolute quantitative results simply because they use underlying numerical values such as OD or S/CO. A change from 0.3 OD to 0.15 OD does not necessarily indicate a twofold decrease in antibodies. Quantitative assays would need additional supporting information such as Limit of Quantitation, linearity/variability across the assay dynamic range, and ideally an external consensus reference standard material for the assay target.
 - b. Precision data is not available for the assays as they were performed at the time of the trials. If the assay variability is not established, it is not clear what amount of observed signal change is within the expected run-to-run variability.
 - c. The use of assay calibrators and controls was not always clear. We note also that both RCTs took place prior to the production of the WHO International Reference Standards for antibodies to *T. cruzi* (2011), which is reference standard material intended for assay quality control and harmonization.

Discussion of conventional versus non-conventional serology assays

12. Conventional serology assays are the traditional ELISA, IFA, and IHA assays that use whole organisms or crude lysates as capture antigens. These assays have been used to screen populations for exposure, are known to detect antibodies that can persist for

years after a *T. cruzi* infection, and can show some cross reactivity with antibodies produced from other infections (e.g., *Leishmania*). For these reasons, conventional assays are usually interpreted in a “two-out-of-three” algorithm using assays with different antigens/formats. Fluctuations in individual conventional serological results (e.g., increases, decreases, and occasional seroconversions between positive and negative) have been described as part of the evolution of antibody responses in untreated patients over time.¹

In the context of the submission, non-conventional assays use select recombinant or purified parasite antigens. The F29 ELISA (Sosa-Estani trial) uses a recombinant preparation of the F29 calcium binding protein that was previously identified in *T. cruzi* epimastigotes. The AT ELISA (De Andrade trial) uses purified F2/3 antigens from *T. cruzi* trypomastigotes which are produced in the course of human infection. It is proposed that the AT ELISA detects host antibodies that have the ability to lyse parasites in the presence of complement (lytic antibodies). Previous studies that measured lytic antibodies directly in complement-mediated lysis assays proposed that lytic antibodies detect live trypomastigotes during infection, and that these lytic antibodies do not persist after the resolution of infection.

13. Benefits and risks of non-conventional assays. One goal of using selected antigens in non-conventional assays would be to improve assay specificity by reducing or eliminating cross reactivity with samples from other infections. Another goal would be to develop assays that have outputs that change more rapidly in response to therapy, and that might therefore serve as surrogate markers to distinguish active from past (resolved) infections. The risks of using assays that are developed from only a select complement of antigens are that the assays may be less sensitive, that they may miss important subpopulations of antibody signal, and that they may be more susceptible to regional differences in circulating parasite strains/antigens.²
14. F29 ELISA and AT ELISA results. In both trials, both non-conventional assays (AT ELISA and F29 ELISA) produced more seronegative conversions in the benznidazole treated group versus the placebo group. The association is supportive of a general drop in antibody levels described by conventional serology assays; however, it is not clear how well negative results from either of the non-conventional assay predict which subjects will be clinical treatment successes. This predictive value would be needed to consider either non-conventional assay result as a primary surrogate endpoint for treatment efficacy.

Other sources of uncertainty and points for consideration:

- a. If a non-conventional assay that uses fewer antigens happens to be less sensitive than a conventional assay, it is possible that the non-conventional assay could produce a negative result following an overall reduction in antibody levels, even when that antibody reduction was not associated with clinical benefit.

¹ Cerisola et al. Rev. Inst. Med. Trop. Sao Paulo (1970) 12:403

² Umezawa, et al. J. Clin. Micro. (1999): 1554

- b. If the ability to detect lytic antibodies is accepted by CDER as evidence of active infection and the inability to detect lytic antibodies is accepted as evidence of sterile cure, there are still some questions that remain about interpreting AT ELISA results. If the AT ELISA does not detect all lytic antibodies, or if there are differences in AT ELISA performance with parasite infections from different regions, an endpoint based on this assay could overestimate drug performance.

Digital Signature Table	
Noel Gerald, Ph.D. Scientific Reviewer DMD/OIR/CDRH	Noel J. Gerald -S 2017.06.07 16:07:25 -04'00'
Kathleen Whitaker, Ph.D. Scientific Reviewer DMD/OIR/CDRH	 Kathleen B. Whitaker -S 2017.06.07 17:06:42 -04'00'
David Goodwin, Ph.D. Scientific Reviewer DMD/OIR/CDRH	 David G. Goodwin -S 2017.06.07 18:05:47 -04'00'
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/s/

GREGORY F DIBERNARDO

06/09/2017

On Behalf of CDRH Consult Review Team for NDA 209570

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 25, 2017
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209570
Product Name and Strength:	Benznidazole tablet 12.5 mg tablet and 100 mg tablet
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Chemo Research, S. L.
Submission Date:	December 29, 2016 and April 7, 2017
OSE RCM #:	2016-3001
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm D
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 REASON FOR REVIEW

The Division of Anti-Infective Products (DAIP) requested that we review the proposed container label, carton labeling, and prescribing information (PI) for benznidazole tablets, under NDA 209570 (See Appendix G) to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

On December 29, 2016, Chemo Research, S. L. submitted a New Drug Application (NDA 209570) for benznidazole tablets. The Applicant's primary proposed proprietary name, (b) (4) ***, was found unacceptable on March 17, 2017. Subsequently, on April 7, 2017, the Applicant submitted a new request for proprietary name review and revised labels and labeling to reflect the proposed proprietary name, (b) (4) ***.

We performed a risk assessment of the proposed container label, carton labeling and Prescribing (PI) Information for benznidazole tablets to identify deficiencies that may lead to medication errors and for areas that could be improved.

Prescribing Information (PI)

Our review of the *Dosage and Administration, Dosage Forms and Strengths and How Supplied* sections of the PI identified areas that could be improved to prevent medication errors. We note that the "Dosage Forms and Strength" section of the Highlights and section 11, *Description*, of the PI describe the benznidazole 100 mg tablets as " (b) (4) scored. It is debossed with the letter, "E", on one side of each quarter portion". However, the product labeling does not indicate that the benznidazole 100 mg tablets have functional scoring. The use of the term *functional scoring* in the labeling can communicate to healthcare providers that the product has been evaluated

against the established criteria^a. Additionally, such labeling should appear in all of the following sections of the prescribing information: “Dosage Forms and Strength” section of the Highlights, “Dosage Forms and Strength” section of the Full Prescribing Information and “How Supplied” section of the Full Prescribing Information.

We acknowledge that benznidazole has weight based dosing and is available as (b) (4) scored tablets. Benznidazole 100 mg tablets can be split into one-half or one-quarter at the score, which may allow physicians to prescribe doses of 25 mg, 50 mg, or 75 mg using the 100 mg tablet. The proposed PI states that benznidazole tablets may be made into a slurry using water for the pediatric population with (b) (4) body weight. We are concerned that the volume of water needed to prepare the slurry is not stated in the PI. The preparation directions for slurry need to be further clarified.

We have provided recommendations in section 4.1.

Container Label and Carton Labeling

In our review of the container labels and carton labeling for Benznidazole 12.5 mg tablets and Benznidazole 100 mg tablets, we found the container labels and carton labeling are not adequately differentiated. We are concerned that this may contribute to product selection errors leading to dispensing and administration of the wrong strength, wrong dose, or both (See Appendix G). We also identified areas that could be improved to increase clarity, prominence, and readability of important safety information. We also note the net quantity statement is in close proximity to the product strength statement. The product is available as 12.5 mg and 100 mg tablet strengths in quantities of 100. A user could mistakenly read the quantity of 100 as the strength for the 12.5 mg tablets. This type of error is supported by postmarket medication error reports. In section 4.2, we provide recommendations to mitigate dosing confusion and promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

The labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product (See section 4.1 and section 4.2).

4.1 RECOMMENDATIONS FOR THE DIVISION

We advise implementation of the following recommendations prior to approval:

A. General comment:

1. If the Office of Pharmaceutical Quality determines that benznidazole 100 mg product has been evaluated and meets the established criteria for scoring, add the term, ‘functional scoring’ in the labeling to communicate to healthcare providers that the benznidazole 100 mg product has been evaluated against the established criteria for scoring^b.

^a Guidance for Industry: Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation. 2013. Available from: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269921.pdf>

^b Guidance for Industry: Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation. 2013. Available from <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269921.pdf>

B. See Appendix F for recommendations for the PI.

4.2 RECOMMENDATIONS FOR CHEMO RESEARCH, S. L.

We refer you to the Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

We recommend the following be implemented prior to approval of this NDA 209570:

1. We note the proposed container label and carton labeling for Benznidazole 12.5 mg tablets and Benznidazole 100 mg are almost identical. Look-alike container labels and carton labeling may contribute to product selection errors leading to dispensing and administration of the wrong strength and/or wrong dose. Revise container label and carton labeling to differentiate between Benznidazole 12.5 mg tablets and Benznidazole 100 mg tablets. Consider the use of different graphics or colors. Each strength should be assigned a unique color.
2. As Currently presented, the net quantity statement (100 tablets) is listed under the strength presentation (12.5 mg and 100 mg) on the container labels. Relocate the net quantity statement away from the product strength. From post-marketing experience, we have learned that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement .
3. For clarity add dosage form "Tablets" to appear on the principal display panel next to the drug name as follow: [Drug] [Dosage Form].
4. Ensure that the product code in the National Drug Code (NDC) numbers, middle 4 digits (XXXX), are unique and non-sequential between the strengths to promote safe use of this product .

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for benznidazole that Chemo Research, S. L. submitted on December 29, 2016.

Table 2. Relevant Product Information for Benznidazole	
Initial Approval Date	N/A
Active Ingredient	benznidazole
Indication	treatment of Chagas disease
Route of Administration	oral
Dosage Form	tablet
Strength	100 mg tablet and 12.5 mg tablet.
Dose and Frequency	(b) (4)
How Supplied	- Benznidazole 100 mg tablets -- available in packages of 100 tablets. - Benznidazole 12.5 mg tablets -- available in packages of 100 tablets.
Storage	Store at controlled room temperature 20° to 25°C (68° to 77°F). Keep bottle tightly closed and protect from moisture. (b) (4)
Container Closure	bottles

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

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SEVAN H KOLEJIAN
05/25/2017

OTTO L TOWNSEND
05/25/2017

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 5/5/2017

TO: Division of Anti-Infective Products
Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209570

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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

/s/

SHILA S NKAH
05/17/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209570	NDA Supplement #: N/A	Efficacy Supplement Category: N/A
Proprietary Name: (b) (4) Established/Proper Name: Benznidazole Dosage Form: Tablet Strengths: 100 mg & 12.5 mg Route of Administration: Oral		
Applicant: Chemo Research, S.L. Agent for Applicant: Exeltis USA, Inc.		
Date of Application: December 29, 2016 Date of Receipt: December 29, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: August 29, 2017		Action Goal Date: Same
Filing Date: February 27, 2017		Date of Filing Meeting: February 21, 2017
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME)		
Proposed indication: Treatment of Chagas disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2) NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		☐ 351(a) ☐ 351(k)
Review Classification: <i>The application will be a priority review if:</i> - A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) - The product is a Qualified Infectious Disease Product (QIDP) - A Tropical Disease Priority Review Voucher was submitted - A Pediatric Rare Disease Priority Review Voucher was submitted		☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products	

☐ Other (drug/device/biological product)				
☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number: PIND 118976				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		Verified 2/20/17
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	☒	☐		Verified 2/20/17
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		Verified 2/20/17
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	☒	☐																		
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		No approved RLD																
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☒																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <th style="width: 20%;">Application No.</th> <th style="width: 30%;">Drug Name</th> <th style="width: 20%;">Exclusivity Code</th> <th style="width: 30%;">Exclusivity Expiration</th> </tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☒		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a

505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?

Check the Electronic Orange Book at:

<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒		Verified Chemo Research, S.L., 4/14/14
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?	☐	☐	☒	
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐	
If yes , # years requested: 5				
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	Verified with FDA CMC
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☐	

If yes, contact the Orange Book Staff (CDER-Orange Book Staff).				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☒	
If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager				
Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ eCTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)	☒	☐		
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☒	
If yes , BLA #				

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> <i>Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	☒	☐	☐	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☐	☒		Orphan Designation
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u>				

Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	Submitted on 1/5/17
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	OSE RPM Informed
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒	☐	☐	Nonclinical reviewer confirmed information was submitted
For applications submitted on or after June 30, 2015:	☐	☐	☒	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

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If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	Consulted on 2/21/17
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	CDRH on 1/18/17, OSI Pending
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting? Date: None	☐	☒		
Pre-NDA meeting?	☒	☐		

Date: September 30, 2016				
Any Special Protocol Assessments (SPAs)? Date: None	☐	☒		

MEMO OF FILING MEETING**DATE:** February 21, 2017

BACKGROUND: NDA 209570 was submitted by Chemo Research, S.L. (foreign applicant) and has selected Exeltis USA, Inc., as their U.S. Agent. The Applicant is requesting an 8 month Priority Review for NDA 209570 for (b) (4) (benznidazole) Tablets 100 mg and 12.5 mg. Previous information on this NDA can be found under PIND **118976**. This product was granted Orphan Product Designation however; an Advisory Committee is not planned for this NDA. NDA 209570 was submitted on 12/29/16; the PDUFA goal date is 8/29/17. The Applicant has requested a Tropical Disease Priority Review Voucher (TDPR) for this application.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gregory DiBernardo	Y
	CPMS:	Maureen Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	Thomas Smith		Y
Division Director/Deputy	Sumathi Nambiar, Director		Y
	Dmitri Iarikov, Acting Deputy Director		Y
Office Director/Deputy	Edward Cox, Director		Y
	John Farley, Deputy Director		Y
Clinical	Reviewer:	Maria Allende	Y
	TL:	Thomas Smith	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Shukal Bala	Y
	TL:		
Clinical Pharmacology	Reviewer:	Abhay Joshi	Y
	TL:	Yongheng (Eric) Zhang	Y
• Genomics	Reviewer:	Not Applicable	
• Pharmacometrics	Reviewer:	Not Applicable	
Biostatistics	Reviewer:	Felicia Griffin	Y

	TL:	Karen Higgins	Y
Nonclinical Pharmacology/Toxicology)	Reviewer:	James Wild	Y
	TL:	Terry Miller	Y
Statistics (carcinogenicity)	Reviewer:	Not Applicable	Y
	TL:	Not Applicable	
Product Quality (CMC) Review Team:	ATL:	Dorota Matecka	Y
	RBPM:	Luz Rivera	N
• Drug Substance	Reviewer:	Yong Wang	N
• Drug Product	Reviewer:	Catherine Windsor	N
• Process	Reviewer:	Jiao Yang	N
• Microbiology	Reviewer:	Jiao Yang	N
• Facility	Reviewer:	Cassandra Abellard	Y
• Biopharmaceutics	Reviewer:	Gerlie Gieser	Y
	TL:	Elsbeth Chickhale	N
• Immunogenicity	Reviewer:	Not Applicable	
• Labeling (BLAs only)	Reviewer:	Not Applicable	
• Other (e.g., Branch Chiefs, EA Reviewer)	Bala Shanmugam, Kasturi Srinivasachar, Steven Frisbee, Derek Smith		N N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sevan Kolejian	Y
	TL:	Vicky Borders-Hemphill	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:	Doris Auth	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	John Lee	N
	TL:	Jan Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	Katherine Schuman, Associate Director for Regulatory Affairs OAP		Y
	Joseph Toerner, Deputy Director for Safety		Y
	Susmita Samanta, Safety RPM		Y
	Abimbola Adebawale, ADL DAIP		Y
	John Lazor, Director OB IV		Y
	Jeffrey Florian, Team Leader OB IV		Y
	Noel Gerald, Reviewer CDRH		Y
	David Goodwin, Reviewer CDRH		Y

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO Report LPRI747-DOC006, comprised of data from two studies - Raaflaub and Ziegler (1979) and #LPRI747/101, was submitted as a historical comparison of bioavailability between Hoffman-Roche formulation, Ranadil® (benznidazole) and the Chemo (benznidazole) 100mg tablet product. This report serves as the basis of the exposure bridge between the Chemo (benznidazole) 100 mg tablet and Ranadil® (benznidazole) product, which was used in cited literature submitted in support of the 505(b)(2) NDA.
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO

Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments
CLINICAL Comments: Information Request to be sent before 74 Day Letter date.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: Applicant Headquarter will be inspected not site inspections.	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments: No Comment for 74 Day Letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments: No Comment for 74 Day Letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: No Comment for 74 Day Letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: Information Request will be sent separately from 74 Day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments: Not Applicable	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within <u>2 months</u> after receipt of the original application? • If so, were the late submission components all submitted within <u>2 months</u>?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 60 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application? Comment: IR was sent to determine location of published literature studies	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: John Farley, Deputy Office Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 29, 2017 21st Century Review Milestones: (listing review milestones in this document is optional): Filing date: 2/27/17, 74 Day Letter date: 3/13/17, Post Mid-Cycle communication: 4/12/17, Labeling PMR/PMC communication: 5/28/17, Late Cycle Meeting Date: 6/29/17, Wrap Up Meeting Date: 7/25/17. Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

GREGORY F DIBERNARDO
03/09/2017

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209570

Application Type: New NDA

Drug Names/Dosage Form: (b) (4) (benznidazole) Tablets 100 mg and 12.5 mg

Applicant: Chemo Research, S.L.

Receipt Date: December 29, 2017

Goal Date: August 29, 2017

1. Regulatory History and Applicant's Main Proposals

This NDA was previously reviewed by FDA as PIND 118976. The applicant is proposing this NME NDA as a 505(b)(2). The applicant has also requested priority review and is seeking approval for the treatment of Chagas disease. This NDA is being reviewed under the PDUFA V Program.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.

Selected Requirements of Prescribing Information

Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

YES

3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

YES

4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES

5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES

6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES

7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Selected Requirements of Prescribing Information

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “***See full prescribing information for complete boxed warning.***”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS

Selected Requirements of Prescribing Information

AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Selected Requirements of Prescribing Information

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS.”** This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading **“FULL PRESCRIBING INFORMATION: CONTENTS*”** must be followed by an asterisk and the following statement must appear at the end of the TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:
-

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “ Labor and Delivery ”)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “ Nursing Mothers ”)
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

N/A

Selected Requirements of Prescribing Information

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

GREGORY F DIBERNARDO
03/09/2017