

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213464Orig1s000**

**OTHER REVIEW(S)**

# MEMORANDUM

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

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DATE: July 27, 2020

TO: Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infective Products (DAIP)  
Office of New Drugs (OND)

FROM: Sripal Reddy Mada, Ph.D.  
Pharmacologist  
Division of Generic Drug Study Integrity (DGDSI)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.  
Director  
Division of Generic Drug Study Integrity (DGDSI)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Information Request (IR) response from Bayer HealthCare Pharmaceuticals, Inc., Germany in reference to the data generated from (b) (4)  
(b) (4) for NDA 213464

### 1. Executive Summary

The Office of Study Integrity and Surveillance (OSIS) initiated Remote Record Review (RRR) of the study 16027-CHICO part-1 (NDA 213464, Lampit (Nifurtimox or BAY A2502) Tablets) conducted at (b) (4)

However, the (b) (4) stated that they were unable to participate in an RRR due to very limited availability of staff under COVID-19 health emergency and commitment to support COVID-19 diagnosis. Therefore, we submitted an IR to the RD to be sent to Bayer HealthCare Pharmaceuticals, Inc.

I did not observe objectionable findings after the review of IR response.

#### 1.1. Recommendation

Based on my review of the response to IR, I conclude the data from the reviewed study is reliable to support a regulatory decision.

## 2. Study for Review

**Study 16027-CHICO part-1 (NDA 213464):** "Prospective, historically controlled study to evaluate the efficacy and safety of a pediatric formulation of nifurtimox in children aged 0 to 17 years with Chagas disease"

### **Assays used in the study:**

- Determination of reactivity for recombinant antigen, total purified antigen, and nonconventional antigen F-29 using ELISA
- Determination of quantitative PCR
- Determination of concentrations of *Trypanosoma cruzi* using an indirect hemagglutination assay (IHA)

**Sample Analysis Dates:** Jan 2016 - Aug 2018

## 3. Scope of Review

OSIS scientist, Sripal Reddy Mada, Ph.D., initiated RRR for the study 16027-CHICO part-1 (NDA 213464, Lampit (Nifurtimox or BAY A2502) Tablets) conducted at (b) (4)

(b) (4) The OSIS sent an invitation letter to the site, requesting voluntary participation in RRR (June 01, 2020, June 04, 2020, June 09, 2020 and June 12, 2020).

However, in their response dated on June 19, 2020, (b) (4) (b) (4) stated that they are unable to participate in an RRR due to COVID-19. Therefore, we reached out to Bayer HealthCare Pharmaceuticals, Inc. on July 07, 2020, by IR to get additional information for the study 16027-CHICO part-1.

My evaluation of the Bayer's IR response dated on July 16, 2020 (**Attachment #1**) is presented below.

**IR item #1:** Please provide the quality assurance procedures taken by Bayer Healthcare Pharmaceuticals, Inc. as a sponsor for the study to ensure that the data generated from (b) (4) (b) (4) are accurate.

**Bayer's Response:** In their response Bayer said that the audit types and frequency were defined for study 16027-CHICO part-1 following a risk assessment and according to their SOP. The audit approach for (b) (4) is described in the Study Audit Plan (**Attachment #2**).

(b) (4) for NDA 213464

Bayer performed site audit at (b) (4) in November 24-25, 2016. During the audit, Bayer covered the following areas: equipment inventory / certification / management / controls, lab materials / supply kits / samples management, analysis (ELISA and PCR), requisition forms, results report, disaster recovery / contingency plan. Also, covered accreditations, Quality Management System, document management, issue and CAPA management, vendor management and oversight, organization / roles / responsibility and training management, computer systems and servers and archives.

In addition, Bayer performed audit at (b) (4) facilities in (b) (4) during November 21 to December 05, 2017 remotely and on-site. (b) (4) is responsible for monitoring and study management after initial site audit by Bayer. In addition, Bayer conducted audit at (b) (4) in January 30-31, 2017. (b) (4) is responsible for EDC (electronic data capture) and data management and submitted to Bayer.

OSIS Evaluation: The Bayer's response is acceptable. I reviewed the Study Audit Plan and site monitoring results (see the IR item #5 response) that was submitted by Bayer and I did not find any issues.

**IR item #2:** If there were samples that were reanalyzed during the two conventional ELISAs for determination of the primary efficacy parameters at (b) (4), please provide the information on the reanalyzed samples and reasons why the samples were reanalyzed. In addition, please provide the original and reanalyzed values.

Bayer's Response: In their response Bayer said that the samples from four analytical runs were reanalyzed due to:

1. Discordant results for the recombinant ELISA and the total purified antigen ELISA (subjects (b) (6)).
2. Dispense error with the conjugate (subjects (b) (6)).
3. Assay validation criteria not met for recombinant ELISA (subjects (b) (6)).

(b) (4)

for NDA 213464

(b) (6)

Bayer provided the source records containing daily events during analysis (translated to English) and is provided as **Attachment #3**. In addition, Bayer provided the raw data of the original and reassayed values for determination of the primary efficacy parameter (values from Visits 1 and 11) from recombinant ELISA and total purified antigen ELISA methods (see **Attachment #4**).

OSIS Evaluation: The Bayer's response is acceptable. I reviewed source records from documenting daily events that was submitted by the Bayer, and I did not find any issues.

**IR item #3: Please provide protocol or SOP deviations that occurred during the study sample analyses by ELISA at (b) (4) if any, and please provide the information how the (b) (4) treated the incidents.**

Bayer's Response: In their response Bayer said there were no protocol or SOP deviations that occurred during the study sample analyses.

OSIS Evaluation: The Bayer's response is adequate.

**IR item #4: Please provide information on the procedures how (b) (4) maintained and controlled the quality of data generated from the sample analyses from the study #16027-CHICO.**

Bayer's Response: In their response Bayer referred to "Module 5.3.5.1 - (16027) (b) (4) Documentation of Methods" of the original NDA for the procedures how (b) (4) maintained and controlled the quality of data generated from the sample analyses from the study #16027-CHICO.

OSIS Evaluation: I reviewed (b) (4) Documentation of Methods" from the original submission, and I did not find any issues.

**IR item #5: If Bayer Healthcare Pharmaceuticals had monitored (b) (4) please provide the site monitoring results.**

(b) (4) for NDA 213464

Bayer's Response: In their response Bayer provided monitoring activities to oversee the tasks of (b) (4) in study #16027-CHICO. Bayer stated that the relevant personnel from (b) (4) took part in the investigator meetings; relevant documentation about the methods used in study #16027-CHICO were reviewed by Bayer; the number of the sampling kits shipped by (b) (4) to the clinical investigator sites, as well as lists of samples received and analyzed by (b) (4) and transfer of lab test results were reviewed by Bayer periodically; relevant personnel from (b) (4) took part in the regular study team meetings and exchange of information like sample shipments from the clinical investigator sites to (b) (4) analyses of the samples and transfer of the laboratory test results to Data Management; and sample tracking reports were provided to Bayer's Study Medical Expert on a monthly basis and the Study Medical Expert performed a medical review of the reports on the serology test results.

OSIS Evaluation: The Bayer's response is adequate. Bayer provided the steps and monitoring activities to oversee the tasks of (b) (4) in study #16027-CHICO. Based on the monitoring activities Bayer has undertaken including investigator meetings, monitoring supply, transfer of test results and medical review of the reports, I am in an opinion that the data generated at (b) (4) and presented in the final bioanalytical report should be reliable.

#### 4. Conclusion

After review of the sponsor's IR response, I conclude that data from the reviewed study is reliable.

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza  
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas  
OTS/OSIS/DGDSI/Cho/Choi/Skelly/Au/Mada

Draft: SRM 07/23/2020; 7/24/2020

Edit: HI 07/23/2020; SC 7/23/2020; 07/24/2020

ECMS: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839da739>

OSIS File: (b) (4)

**FACTS:** (b) (4)

Sripal Reddy Mada, Ph.D.  
Pharmacologist

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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)

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Date of This Memorandum:	July 24, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213464
Product Name and Strength:	Lampit (nifurtimox) Tablets, 30 mg and 120 mg
Applicant/Sponsor Name:	Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
OSE RCM #:	2019-2503-3
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 24, 2020 for Lampit. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Lampit (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.<sup>a</sup>

## 2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

(b) (4)

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<sup>a</sup> Myers, D. Label and Labeling Review Memo for Lampit (NDA 213464). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 21. RCM No.: 2019-2503-2.

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**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Sufficiency of ARIA to Evaluate the Association between Nifurtimox Exposure and Risks  
of Pregnancy, Maternal, Fetal/Neonatal and Infant Outcomes**

Date: July 23, 2020

Acting Team Leader: Natasha Pratt, PhD  
Division of Epidemiology II

Acting Deputy Director: Monique Falconer, MD, MS  
Division of Epidemiology II

OPE Deputy Director: Michael D. Blum, MD, MPH

FDA Sentinel Team Lead: Michael D. Nguyen, MD

OSE Deputy Director: Robert Ball, MD, MPH, ScM

Subject: Sufficiency of ARIA to evaluate the association between  
nifurtimox exposure and risks of pregnancy, maternal,  
fetal/neonatal and infant outcomes.

Drug Name(s): Nifurtimox

Application Type/Number: NDA 213464

Applicant/sponsor: Bayer

OSE RCM #: 2020-1362

## **1. BACKGROUND INFORMATION**

### **1.1. Medical Product**

On December 6, 2019, Bayer HealthCare Pharmaceuticals Inc., submitted a New Drug Application for Lampit (nifurtimox) tablets, NDA 213464, for the treatment of Chagas disease in term newborns, infants, children and adolescents less than 18 years of age.

Chagas disease is a serious disease affecting eight million individuals worldwide and at least 300,000 in the United States. Although patients can be asymptomatic for years, disease manifestations of Chagas disease can be life-threatening and include sudden cardiac death and heart failure. Benznidazole is the only approved treatment for Chagas disease in the United States.

Nifurtimox is not currently approved in the United States; however, it can be obtained from the Parasitic Disease Drug Service under an investigational protocol from the Centers for Disease Control and Prevention (CDC).<sup>a</sup> It also has been marketed outside of the United States for several decades.

### **1.2. Describe the Safety Concern**

Nifurtimox has been shown to have significant embryofetal toxicity in animals, including fetal malformations in rabbits (fusion of caudal vertebral bodies and ventricular septal defects).<sup>b</sup> Data from the phase 3 clinical study<sup>c</sup> submitted by the Applicant only reported five pregnancies during the study period,<sup>d</sup> which are insufficient to determine a drug-associated risk of miscarriage, major congenital anomalies or maternal or fetal adverse effects. Due to the high degree of embryofetal toxicity seen in animal studies, nifurtimox labeling will note this risk in the following sections of the label:

- **2. Dosage and Administration** (subsection 2.3)
- **5. Warnings and Precautions** (subsection 5.2: Embryofetal Toxicity)
- **8. Use in Specific Populations** (subsections 8.1: Pregnancy; 8.3: Females and Males of Reproductive Potential [pregnancy testing and contraception])

Available literature suggests a Disease-Associated Maternal and/or Embryo/Fetal Risk with acute symptomatic Chagas disease during pregnancy; therefore, a “Clinical Considerations” regarding this indication will be included for labeling (subsection 8.1).

According to CDC, in the United States approximately 40,000 women of reproductive age are infected with Chagas disease. Treatment for chronic Chagas disease during pregnancy is typically delayed until after pregnancy; however, it is possible that a female of reproductive potential could have an unintended pregnancy while taking nifurtimox for treating chronic

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<sup>a</sup> Antiparasitic Treatment. Centers for Disease Control and Prevention.

[https://www.cdc.gov/parasites/chagas/health\\_professionals/tx.html](https://www.cdc.gov/parasites/chagas/health_professionals/tx.html), accessed July 5, 2020.

<sup>b</sup> The reader is referred to the Pharmacology/Toxicology review by James Wild, Ph.D., and Terry Miller, Ph.D.

<sup>c</sup> Study 16027 was a randomized double-blind study of pediatric subjects from birth to <18 years old with asymptomatic Chagas disease

<sup>d</sup> Outcome of the five pregnancies: three live births of healthy infants, one infant with health problems (neonatal hypoglycemia and fetal growth restriction with low birth weight) that were deemed not related to study drug and one elective abortion with unspecified reason.

Chagas disease. It was estimated that about half (45%) of pregnancies are unintended annually in the United States.<sup>e</sup> Considering that nifurtimox has the potential for use among females of reproductive potential, gathering additional pregnancy exposure data is important to assess the safety of this drug during pregnancy.<sup>f</sup>

The Division of Pediatric and Maternal Health (DPMH) recommends a post-marketing requirement (PMR) for a Single-Arm Pregnancy Safety Study. A single-arm pregnancy safety study is appropriate because this drug carries a warning of embryo-fetotoxicity in the label, and the exposure during pregnancy is expected to be low. Language regarding the Pregnancy Safety Study will be included in subsection 8.1 of labeling.

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

*Purpose (place an "X" in the appropriate boxes; more than one may be chosen)*

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

### 2.2. Regulatory Goal

- ☒ Signal detection – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

### 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review

<sup>e</sup> Finer LB and Zolna MR, Declines in unintended pregnancy in the United States, 2008–2011, New England Journal of Medicine, 2016, 374(9):843–852, doi:10.1056/NEJMsa1506575

<sup>f</sup> June 30, 2020, DPMH review for LAMPIT (nifurtimox), Carrie Ceresa, Pharm D., MPH, DARRTS Reference ID 4633593



- ☐ Electronic database study without chart review
- ☒ Other, please specify: *Single-arm pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives as needed. These studies do not require inferential analyses and do not have the sample size requirements of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug carries a warning of embryo-fetotoxicity in the label, and the exposure during pregnancy is expected to be low, thus, the study is not required to be sufficiently powered for a comparative analysis.*

**2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?**

- ☐ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☐ Covariates
- ☒ Analytical Tools

*For any checked boxes above, please describe briefly:*

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

**2.5. Please include the proposed PMR language in the approval letter.**

The PMR to be issued for nifurtimox is as follows:

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to LAMPIT (nifurtimox) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years.

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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)

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Date of This Memorandum:	July 21, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213464
Product Name and Strength:	Lampit (nifurtimox) Tablets, 30 mg and 120 mg
Applicant/Sponsor Name:	Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
OSE RCM #:	2019-2503-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

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## 1 PURPOSE OF MEMORANDUM

As currently presented, the language included in Section 16.2, *Storage and Handling*, of the proposed prescribing information (PI)<sup>a</sup>, is not aligned with the most recently reviewed proposed carton labels and container labeling.<sup>b</sup> Therefore, the Division of Anti-Infectives (DAI) requested that we provide recommendations for Bayer to revise their carton labels and container labeling, to align with Section 16.2, *Storage and Handling*, of the proposed PI for Lampit.

In Section 2 below, to address this consistency in labeling that may contribute to confusion that can result in medication error, we provide recommendations for Bayer. We ask that the Division convey Table 1 in its entirety to Bayer Healthcare Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

## 2 RECOMMENDATIONS FOR BAYER HEALTHCARE PHARMACEUTICALS, INC.

Table 1. Identified Issues and Recommendations for Bayer Healthcare Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)
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<sup>a</sup> Draft Labeling Text – Clean: (nifurtimox NDA 213464). Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2020 MAY 15. Available from: [\\cdsesub1\evsprod\nda213464\0034\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean.docx](#).

<sup>b</sup> Myers, D. Label and Labeling Review for Lampit (NDA 213464). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 19. RCM No.: 2019-2503-1.



IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling		
As currently presented, the container labels and carton labeling received on May 15, 2020, includes the statement "Keep bottle tightly closed and protected from moisture." However, this statement on the proposed container labels and carton labeling is inconsistent with the statement included in Section 16.2, <i>Storage and Handling</i> , of the proposed prescribing information (PI), received on May 15, 2020, "Keep bottle with child-resistant closure tightly closed and protect from moisture."	Inconsistent labeling may contribute to confusion that can result in medication error.	To provided consistency between the container labels, carton labeling, and PI, revise the current statement "Keep bottle tightly closed and protected from moisture." on the container labels and carton labeling to "Keep bottle with child-resistant closure tightly closed and protect from moisture."

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

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

**Memorandum**

**Date:** July 7, 2020

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

Abimbola Adebawale  
Associate Director for Labeling  
DAIP

**From:** Zarna Patel, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** James Dvorsky, PharmD  
Team Leader  
OPDP

**Subject:** OPDP Labeling Comments for LAMPIT (nifurtimox) Tablets, for oral use

**NDA:** 213464

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In response to DAIP consult request dated February 27, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for LAMPIT (nifurtimox) Tablets, for oral use (Lampit).

**PI, PPI and IFU:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP (Gregory DiBernardo) on June 29, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on July 7, 2020.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 15, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or [zarna.patel@fda.hhs.gov](mailto:zarna.patel@fda.hhs.gov).

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

**PATIENT LABELING REVIEW**

Date: July 7, 2020

To: Gregory F. DiBernardo  
Regulatory Project Manager  
**Division of Anti-Infectives (DAI)**

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)**  
  
Zarna Patel, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)  
and Instructions for Use (IFU)

Drug Name (established name): LAMPIT (nifurtimox)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 213464

Applicant: Bayer HealthCare Pharmaceuticals Inc.

## 1 INTRODUCTION

On December 6, 2019, Bayer HealthCare Pharmaceuticals Inc. submitted for the Agency's review a 505(b)(2) original New Drug Application (NDA) 213464 for Accelerated Approval, for LAMPIT (nifurtimox) tablets, for oral use. The proposed indication for LAMPIT (nifurtimox) tablets, for oral use is for the treatment of Chagas disease (American Trypanosomiasis) caused by *Trypanosoma cruzi*, in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on March 31, 2020 and February 27, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for LAMPIT (nifurtimox) tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft LAMPIT (nifurtimox) tablets, for oral use PPI and IFU received on December 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 29, 2020.
- Draft LAMPIT (nifurtimox) tablets, for oral use Prescribing Information (PI) received on December 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 29, 2020.
- Approved BENZNIDAZOLE tablets, for oral use comparator labeling dated August 29, 2017.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading 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 PPI and IFU documents using the Arial font, size 10 and 11 respectively.

In our collaborative review of the PPI and IFU we have:

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

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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Public Health Service

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**Division of Pediatric and Maternal Health Review**

**Date:** June 30, 2020      **Date consulted:** December 13, 2019

**From:** Carrie Ceresa, Pharm D., MPH, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Miriam Dinatale, D.O., Team Leader, Maternal Health, DPMH  
  
Jane Liedtka, MD, Acting Team Leader, Maternal Health, DPMH  
  
Lynne P. Yao, MD, OND, Division Director, DPMH  
Division of Pediatric and Maternal Health

**To:** Division of Anti-Infective (DAI)

**Drug:** LAMPIT (nifurtimox) tablets for oral use

**NDA:** 213464

**Applicant:** Bayer HealthCare Pharmaceuticals Inc.

**Subject:** Pregnancy and Lactation Labeling Formatting Recommendations

**Indication:** for the treatment of Chagas disease caused by *Trypanosoma cruzi* (*T. cruzi*) in term newborns, infants, children and adolescents less than 18 years of age.

**Materials**

**Reviewed:**

- December 6, 2019, New Drug Applications for Lampit (nifurtimox) tablets, NDA 213464
- December 13, 2019, DPMH consult for NDA 213464, PLLR labeling, DARRTS  
Reference ID 4533686

- June 28, 2017, DPMH review for (b) (4) (benznidazole), Jane Liedtka, MD, Medical Officer, DARRTS Reference ID 4117840<sup>1</sup>

### Consult Question:

“In section 8 of the draft product label, the Applicant proposes (b) (4)

The Applicant states that there are no data in pregnant women to inform on drug-associated risk. As noted above, the drug has been in use for at least 30 years outside of the U.S. and also is available through the CDC. We conducted a quick PubMed search, but did not find any useful references related to birth outcomes following treatment during pregnancy.”

### Questions:

1. Are there any published human data on use of nifurtimox during pregnancy?
2. Is the Applicant's (b) (4) warranted?
3. Is a Warning for Embryo-Fetal Toxicity warranted?
4. Do you recommend any additional labeling changes?

## INTRODUCTION AND BACKGROUND

On December 6, 2019, Bayer HealthCare Pharmaceuticals Inc., submitted a New Drug Applications for Lampit (nifurtimox) tablets, NDA 213464, for the treatment of Chagas disease caused by *Trypanosoma cruzi* (T. cruzi) in term newborns, infants, children and adolescents less than 18 years of age. The Division of Anti-Infective (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on December 13, 2019, to assist with the applicant's proposed labeling recommendations in the draft product label in subsection 8.1 Pregnancy.

Nifurtimox is not currently approved in the United States; however, it can be obtained from the Parasitic Disease Drug Service under an investigational protocol from the Centers for Disease Control and Prevention (CDC).<sup>2</sup>

Table 1: Nifurtimox Drug Characteristics<sup>3</sup>

Drug Class	Antiprotozoal
Mechanism of Action (MOA)	MOA is not fully understood; however, it is believed that specific trypanosomal type I nitroreductase catalyzes the reduction of nifurtimox to an unsaturated open-chain nitrile derivative without oxygen demand which has significant growth inhibitory properties against the parasite.
Dose and Administration (D&A) <sup>2</sup>	The D&A instructions below are those recommended by the CDC.

<sup>1</sup> The benznidazole review was part of the material reviewed but was not a source relied upon for the labeling recommendations in this consult review.

<sup>2</sup> Antiparasitic Treatment. Centers for Disease Control and Prevention.

[https://www.cdc.gov/parasites/chagas/health\\_professionals/tx.html](https://www.cdc.gov/parasites/chagas/health_professionals/tx.html), accessed 24 March 2020.

<sup>3</sup> Nifurtimox Product Insert.

	<div> <div>≤ 10 years</div> <div>15–20 mg/kg per day orally in 3 or 4 divided doses for 90 days</div> </div> <div> <div>11–16 years</div> <div>12.5–15 mg/kg per day orally in 3 or 4 divided doses for 90 days</div> </div> <div> <div>17 years or older</div> <div>8–10 mg/kg per day orally in 3 or 4 divided doses for 90 days</div> </div>
Molecular Weight	287.29 Daltons
Protein Binding	58% fraction unbound in human plasma
Terminal Half-Life	<b>Fed conditions:</b> 4x 30 mg tablets: 2.63/23.1 hours; 1 x 120 mg tablets: 2.85/30.2 hours; 4 x 30 mg dissolved tablets : 3.61/37.3 hours; <b>fasted conditions:</b> 4x 30 mg tablets 3.07/34.6 hours
Bioavailability	Increased when given with food; refer to the Applicant's proposed package insert
Warnings and Precautions	Neurological and psychiatric conditions; hypersensitivity; (b) (4); decreased appetite and weight loss, (b) (4)
Adverse Reactions	Headache, vomiting, nausea, decreased appetite, pyrexia, abdominal pain

## REVIEW

### PREGNANCY

#### Chagas Disease and Pregnancy<sup>4</sup>

- Chagas disease (CD), 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.<sup>5</sup>
- Six to seven million people are estimated to have CD, and 25,000 CD-related deaths occur each year in the world.<sup>6,7</sup> 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 States.<sup>8</sup> Infection is life-long in the

<sup>4</sup> June 28, 2017, DPMH review for (b) (4) (benznidazole), Jane Liedtka, MD, Medical Officer, DARRTS Reference ID 4117840

<sup>5</sup> WHO technical report 2008.

<sup>6</sup> 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.

<sup>7</sup> World Health Organization. Chagas disease. [<sup>8</sup> Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. Clin Infect Dis 2009; 49\(5\): e52-e54.](https://www.who.int/news-room/facts-in-pictures/detail/chagas-disease#:~:text=Chagas%20disease%2C%20also%20known%20as,parasite%20that%20causes%20Chagas%20disease, Accessed 24 June 2020.</a></p>
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absence of effective treatment. The most important consequence of *T. cruzi* infection is cardiomyopathy, which occurs in 20 to 30% of infected persons.<sup>9</sup>

- According to the CDC, in the United States approximately 40,000 women of reproductive age are infected with CD, and treatment during pregnancy with benznidazole or nifurtimox is typically delayed until after pregnancy. However, according to the CDC, data from 2008 indicate that more than half (51%) of pregnancies are unintended and according to the WHO, data from a 2019 study, globally 74 million women living in low and middle income countries have unintended pregnancies annually.<sup>10,11</sup>

*Reviewer comment: Although use of nifurtimox is typically delayed until after pregnancy, it is possible that a female of reproductive potential could have an unintended pregnancy while taking nifurtimox for the treatment of chronic CD.*

- Acute Chagas disease occurs immediately after infection and can last weeks or months. During the acute phase, parasites are found circulating in the blood. This phase is usually mild or asymptomatic. In rare cases, acute infection can cause severe inflammation of the heart muscle or the brain.<sup>12</sup>
- Treatment for CD
  - Acute Infection:
    - The CDC recommends antiparasitic treatment for all cases of acute or reactivated Chagas disease.<sup>2</sup>
  - Chronic Infection:
    - The CDC recommends antiparasitic treatment for chronic *T. cruzi* infection in children up to age 18.
    - Treatment is strongly encouraged for adults up to age 50 with chronic infection who do not have advanced cardiomyopathy. For those older than 50 years the CDC recommends weighing the risk and benefit of treatment per the individual.<sup>2</sup>
    - Published literature and the WHO recommends the treatment of females of reproductive potential with chronic CD to prevent congenital CD. The WHO notes that recent evidence demonstrates that diagnosing and treating females of reproductive potential “can effectively prevent congenital transmission.... Up to now, control and prevention strategies for Chagas disease largely relied on the early detection and treatment of infected newborns and siblings of pregnant women. But a recent shift in approaches to prevent transmission globally – including in non-endemic countries – is through active, systematic screening of girls and women at

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

<sup>10</sup> Centers for Disease Control and Prevention. Unintended Pregnancies. <https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/index.htm>, accessed 24 June 2020.

<sup>11</sup> World Health Organization. High rates of unintended pregnancies linked to gaps in family planning services: New WHO study. <https://www.who.int/news-room/detail/25-10-2019-high-rates-of-unintended-pregnancies-linked-to-gaps-in-family-planning-services-new-who-study>, accessed 24 June 2020.

<sup>12</sup> CDC: Chagas Disease. <https://www.cdc.gov/parasites/chagas/disease.html>. Accessed 6/15/2020.

risk of infection and provides excellent opportunities for prevention of posterior transmission throughout pregnancy and birth.”<sup>13</sup>

- Treatment is recommended for children infected with congenital Chagas disease. Untreated congenital Chagas disease will put infant at risk for developing clinical manifestations of chronic Chagas disease, including cardiac complications (heart failure, enlarged heart, cardiac arrest) and gastrointestinal complications (megaesophagus or megacolon).<sup>14</sup>
- The WHO notes that treatment of chronic infection “is not recommended during pregnancy since the teratogenic risks of the available medications (benznidazole and nifurtimox) are not well understood, the risk of adverse reactions is high in adults ... treatment should only be considered after delivery and breastfeeding.”<sup>13,15</sup>
- Maternal infection can cause adverse effects during pregnancy relating to fetal growth and maturity, abortion, prematurity, increased neonatal mortality and transmission of Chagas Disease.<sup>16,17</sup> 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.<sup>6</sup>
- Only two drugs, nifurtimox and benznidazole are currently available for the treatment of Chagas Disease, both with similar effectiveness and limitations.<sup>18,19</sup> Both drugs are associated with a high risk of adverse events in adults, including dermatologic reactions (ie. toxic epidermal necrolysis), central and nervous system effects (paresthesias, headaches, dizziness), and bone marrow depression (anemia, neutropenia, thrombocytopenia, leukopenia) with benznidazole, and neurologic and psychiatric conditions and hypersensitivity reactions (ie. hypotension, angioedema, dyspnea, rash) with nifurtimox. Benznidazole is the most commonly used drug in South America, due to availability issues.<sup>18</sup>
- Prevalence of vertical transmission of *T. cruzi* infection from immunocompetent women to their fetus varies from 0.1% to 18% among regions,<sup>20</sup> and such transmission is strongly

<sup>13</sup> WHO. “Preventing mother-to-child transmission of Chagas disease: from control to elimination.” November 16, 2018. [https://www.who.int/neglected\\_diseases/news/Chagas-Preventing-mother-to-child-transmission/en/](https://www.who.int/neglected_diseases/news/Chagas-Preventing-mother-to-child-transmission/en/). Accessed 6/29/2020.

<sup>14</sup> Murcia, I et al. Treatment of Infected Women of Childbearing Age Prevents Congenital *Trypanosoma cruzi* Infection by Eliminating the Parasitemia Detected by PCR. The Journal of Infectious Diseases, Volume 215, Issue 9. 2017; 1452-1458.

<sup>15</sup> Howard E, P Buekens, Y Carlier, Current Treatment Guidelines for *Trypanosoma cruzi* infection in Pregnant Women and Infants, Int J Antimicrob Agents, 2012 May;39(5):451-452.

<sup>16</sup> 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.

<sup>17</sup> 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.

<sup>18</sup> Jannin J, Villa L. An Overview of Chagas Disease Treatment. Mem Inst Oswaldo Cruz. 2007; 102 (Suppl 1): 95-7.

<sup>19</sup> 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.

<sup>20</sup> 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.

associated with the maternal blood-parasite load.<sup>9,21</sup> However, patients co-infected with HIV exhibit higher levels of parasitemia and a higher congenital transmission rate than those who are not co-infected.<sup>22</sup> 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, sepsis, myocarditis, hepatitis, meningoencephalitis, edema, fever, anemia, and jaundice. Infected infants are presumed to carry the same 20–30% lifetime risk of cardiac or gastrointestinal disease as other infected individuals.

#### Nonclinical Experience

Nifurtimox administered orally to pregnant mice, rats, and rabbits during organogenesis was associated with reduced fetal body weights in mice, reduced maternal and fetal body weights in rats, and abortions, reduced maternal weight gain, and reduced numbers of live fetuses in rabbits when nifurtimox was administered orally during organogenesis at doses approximately equal to the MRHD in rodents and 2-times the MRHD in rabbits. Increased incidences of fetal skeletal (fusion of caudal vertebral bodies), and visceral (ventricular septal defect of the heart) malformations occurred in rabbits at nifurtimox doses approximately 0.2 and 0.5 times respectively the MRHD. In a pre-postnatal study, maternal body weights and fetal body weights of first generation offspring were reduced at a doses approximately equal to or 0.5 times the MRHD respectively, and several male offspring in the nifurtimox treatment groups exhibited slightly small testes at doses  $\geq 0.2$  times the MRHD. Based on animal studies, nifurtimox crosses the placental barrier. The reader is referred to the Pharmacology/Toxicology review by James Wild, Ph.D., and Terry Miller, Ph.D, DARRTS.

#### Phase 3 Clinical Study 16027

According to the applicant, clinical study 16027, which included a prospective, historically controlled study to evaluate the efficacy and safety of nifurtimox in children 0 to 17 years with Chagas Disease, had five pregnancies reported during the study period. Four of the pregnancies contain follow up information to include two live births of healthy male infants, one male with health problems investigators deemed not related to study drug and one elective abortion. See case narratives below in Table 2.

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<sup>21</sup> Bern C *et al.* Congenital Trypanosoma cruzi transmission in Santa Cruz, Bolivia. Clin Infect Dis. 2009; 49:1667–74.

<sup>22</sup> 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.

Table 2. Pregnancies reported in clinical study 16027

Subject ID	Narrative
(b) (6)	Randomized to the 60-day regimen and completed study treatment on (b) (6). The subject's last menstrual period was on an unspecified date in (b) (6). The subject gave birth to a live, healthy male baby via cesarean section on (b) (6) and completed the study follow-up period on (b) (6).
	Randomized to the 30-day regimen and completed study treatment on (b) (6). On (b) (6), the subject had a positive urine pregnancy test that was confirmed by ultrasound on (b) (6). The subject gave birth to a live, healthy male baby via vaginal birth on (b) (6).
	Randomized to the 30-day regimen and completed study treatment on (b) (6). The subject's pregnancy was confirmed by serum HCG on 10 (b) (6). The subject underwent an elective abortion on (b) (6). The reason for elective abortion was not specified.
	Randomized to the 60-day regimen on (b) (6) and completed study treatment on (b) (6). The subject used the oral contraceptive norethisterone enanthate and estradiol valerate from (b) (6) to (b) (6). Her last menstrual period was on (b) (6). On an unspecified date, pregnancy was confirmed via urine pregnancy test and ultrasound. On (b) (6), the subject gave birth to a live, healthy female baby at 40 weeks via caesarean section. No maternal complications were reported during the pregnancy or delivery. No fetal abnormalities were observed.
	Randomized to the 60-day regimen on (b) (6) and completed study treatment on (b) (6). The subject's last menstrual period occurred on an unspecified date in (b) (6). The subject's previous method of contraception was condoms. Pregnancy was confirmed on the day of birth. On (b) (6), the subject gave birth to a live, male baby with health problems via vaginal delivery. The neonate was diagnosed with neonatal hypoglycemia and fetal growth restriction with low birth weight. At the time of the report, the neonatal hypoglycemia had resolved. The investigator performed an evaluation of the baby and found him healthy for his age, with proper physical and psychomotor development inside the parameters of normality. As such, the noted health problems are not considered clinically significant. The investigator considered fetal growth restriction and neonatal hypoglycemia to be unrelated to nifurtimox.

## Review of Literature

### *Applicant's Review of Literature*

According to the applicant, there are no data on the use of nifurtimox in pregnant women. In addition, the WHO does not recommend treatment with benznidazole or nifurtimox during pregnancy. Based on animal studies the applicant has proposed to contraindicate nifurtimox during the first trimester of pregnancy.

### *DPMH's Review of Literature*

DPMH conducted a search of published literature using PubMed and Embase regarding nifurtimox exposure during pregnancy using the following search terms, “nifurtimox and fetal malformations,” “nifurtimox and spontaneous abortion and miscarriage,” “nifurtimox and embryo-fetotoxicity. In addition to the applicant’s review of literature, no additional relevant data were found for review. Likewise, no information was found in *Drugs in Pregnancy and Lactation* by Briggs and Freeman.<sup>23</sup>

According to Micromedex,<sup>24</sup> “No epidemiological studies of congenital anomalies among infants born to women who were treated with nifurtimox during pregnancy have been reported. No congenital anomalies were observed among the offspring of rats or mice treated orally during pregnancy with nifurtimox in doses 1-6 times the maximum used in humans. Fetal weight was significantly reduced in both species after treatment at the higher doses; this treatment also caused maternal toxicity in the rats.”

*Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH’s opinion of the data submission and recommendations.*

### **LACTATION**

#### Nonclinical Experience

There are no data on the presence of nifurtimox in animal milk.

#### Review of Literature

##### *Applicant’s Review of Literature*

According to the applicant nifurtimox is found in human milk in low concentrations at a median relative infant dose of 6.7% of maternal weight-adjusted dose. The applicant submitted a publication by Moroni et al. (2019),<sup>25</sup> which contains a prospective study of 10 lactating women with Chagas disease treated with nifurtimox for one month. Nifurtimox was measured in plasma and milk, and breastfeeding infants were evaluated during admission, on the 7<sup>th</sup> day of treatment, on the 30<sup>th</sup> days of treatment and monthly for six months. Assuming a 150 mL/kg daily milk intake, the estimated median nifurtimox daily infant dose was 0.50mg/kg/day, which results in a median relative infant dose of 6.7% of the maternal weight-adjusted daily dose. See Table 3 below for nifurtimox levels measured. The infants were evaluated by pediatricians and had no behavioral, central nervous system, growth or weight abnormalities that were attributable to nifurtimox.

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<sup>23</sup> Briggs, GG and Freeman, R., *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk* Online version: <http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi>.

<sup>24</sup> Nifurtimox. Truven Health Analytics LLC. Micromedex.

<sup>25</sup> Moroni S, Marson ME, Moscatelli G, et al. Negligible exposure to **nifurtimox** through breast milk during maternal treatment for Chagas Disease. *PLoS Negl Trop Dis*. 2019;13:e0007647



Table 3. Nifurtimox levels in maternal plasma and breast milk (corresponds to Table 1, Moroni et al., 2019, page 5)<sup>25</sup>

Patient ID*	Maternal NF dose (mg/day)	Maternal NF weight-adjusted dose (mg/kg/day)	Sampling times (days after start of treatment)	Plasma		Breast Milk		Infant daily dose (mg/kg)*	Milk/plasma *	Relative infant NF dose (% weight-adjusted maternal dose) <sup>†</sup>
				Hours after dose	NF concentration (mg/L)	Hours after dose	NF concentration (mg/L)			
P1	720	9.8	9	3.4	LOQ	7	9.5	1.42	190	14.54%
P2	720	12	8	9.42	0.2	7.3	6.2	0.93	31	7.75%
P3	540	9.1	4	5.1	0.2	1	2.3	0.34	11.5	3.79%
P4	540	9.6	10	2.15	1.1	8.58	4.6	0.69	4.18	7.19%
P4	540	9.6	31	13.05	LOQ	13	1.6	—	—	—
P5	540	9.4	9	2.05	0.8	2.58	4.4	0.66	5.5	7.02%
P5	540	9.4	31	11.1	0.2	11.15	2.0	—	10	—
P6	540	8.3	8	2	1.1	1.5	1.3	0.19	1.18	2.35%
P6	540	8.3	31	9.25	LOQ	9.20	0.90	—	18	—
P7	540	10	21	11.5	LOQ	11.45	0.90	0.13	18	1.35%
P7	540	10	31	11.42	LOQ	11.39	0.70	—	14	—
P8	540	9.7	9	2.30	LOQ	1.25	1.4	0.21	28	2.16%
P8	540	9.7	30	9.05	LOQ	9.10	LOQ	—	—	—
P9	540	10	8	9.30	LOQ	9.25	LOD	—	—	—
P9	540	10	31	11.15	ND	11.07	LOD	—	—	—
P10	540	10.3	8	1.16	0.30	1.1	2.50	—	8.33	6.70%
P10	540	10.3	31	10.0	LOQ	9.55	4.6	0.69	92	—
Median**	540	9.75	10	9.25	0.30	9.1	2.15	0.50	16.0	6.70
Inter Quartile Range		[9.45; 10]			[0.2–0.95]		[1.32–4.55]	[0.20–0.69]	[8.75–30.25]	[2.35–7.19]

\*Data from one patient who had both plasma and milk levels below LOD, but later admitted to not taking the medication as prescribed, has been removed from the analysis to avoid confusion

\*\*Whenever 2 measurements were available for the same patient, the highest value was chosen for the estimation of the median, to avoid biasing results by including multiple values from the same patient

ND: Not done

LOQ: Below limit of quantitation

LOD: Below limit of Detection

*Reviewer comment: See clinical pharmacology review below.*

#### *DPMH's Review of Literature*

DPMH conducted a search of published literature using PubMed and Embase regarding nifurtimox exposure during lactation. The available published literature are summarized above as submitted by the applicant and below in the LactMed section. No additional information was found in *Drugs in Pregnancy and Lactation* by Briggs and Freeman,<sup>23</sup> or *Medication and Mothers Milk*.<sup>26</sup>

<sup>26</sup> Hale, Thomas (2017). Medications and Mother's Milk. Amarillo, Texas. Springer Publishing Company LLC.

According to LactMed,<sup>27</sup>

#### *Summary*

“Limited information indicates that maternal doses of nifurtimox up to 15 mg/kg daily produce do not cause any adverse serious effects in breastfed infants. Breastmilk levels and a computer simulation found that the dose that an exclusively breastfed infant would receive through breastmilk would be much less than the dose given to treat Chagas disease in newborn infants. Other authors consider that breastfeeding is not contraindicated during the use of nifurtimox.”<sup>28,29</sup>

#### *Maternal Levels*

“A computer simulation using pharmacokinetic data from adults and assuming milk-plasma ratios of 1 resulted in an estimated median infant dose of 0.19% of the maternal weight-adjusted dosage. Assuming milk-plasma ratios of 6 resulted in an estimated maximum infant dose of 3.1% of the maternal weight-adjusted dosage.”<sup>30</sup>

Four women with Chagas disease were treated with nifurtimox 10 to 15 mg/kg daily in 3 divided doses 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 nifurtimox ranged from nonquantifiable (<0.55 mg/L) to 8.2 mg/L.<sup>31</sup>

Ten women were receiving a median dose of nifurtimox of 9.75 mg/kg daily donated 1 or 2 milk samples at various times after a dose at steady state. The median nifurtimox concentration in milk was 2.15 mg/L (interquartile range 1.32 to 4.55 mg/L). The authors estimated that infants would receive a median daily dosage of 0.5 mg/kg, which is equal to a median weight-adjusted maternal dose of 6.7% (interquartile range 2.35 to 7.19%).<sup>20</sup> (Note to the reader-This is the same article that was reviewed above by the Applicant.)

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<sup>27</sup> <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.

<sup>28</sup> Sankale M, Brun A. Les médicaments des parasitoses tropicales au cours de la grossesse et de l'allaitement. (2 parts). *Le Concours Medical* 1991;14:2335-9; 248-51.

<sup>29</sup> Barennes H, Choonara I. Breast feeding and drug therapy in neglected diseases. *Arch Dis Child*. 2010;95:222–3.

<sup>30</sup> Garcia-Bournissen F, Altcheh J, Panchaud A, et al. Is use of nifurtimox for the treatment of Chagas disease compatible with breastfeeding? A population pharmacokinetics analysis. *Arch Dis Child*. 2010;95:224–8.

<sup>31</sup> Padro JM, Pellegrino Vidal RB, Echevarria RN, 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.

### *Effects in Breastfed Infants*

“A cohort of 33 infants who were breastfed (extent not stated) by hospitalized mothers taking nifurtimox was followed in the Democratic Republic of the Congo. Thirty mothers took a full course of 30 doses of oral nifurtimox 15 mg/kg daily and all received 14 doses of intravenous eflornithine 400 mg/kg daily for 7 days for human African trypanosomiasis. (sleeping sickness). Nursing mothers also took a median of 4 other concomitant medications. No serious adverse events were reported in any of the breastfed infants.”<sup>32</sup>

The DAI clinical pharmacology reviewer assessed the publication by Moroni et al. (2019),<sup>19</sup> and noted the following:

- Within the article, the information supporting the bioanalytical method used in pharmacokinetic (PK) assessments is not adequate for the inclusion of actual nifurtimox concentrations in human milk.
- The inclusion of “...less than 15% of the recommended dose for pediatric Chagas patients...” is a reasonable conservative estimate for Chagas patients based on the information from the literature. However, from a clinical pharmacology perspective, it is not clear how 15% dose would drive risk-benefit balance for healthy newborns/infants.

*Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH’s opinion of the data submission and recommendations.*

## **FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

### Nonclinical Experience

In a study examining the effects of nifurtimox on testicular morphology, male mice fed 0.08% or 0.16% nifurtimox in animal feed for 14 weeks experienced dose-dependent testicular toxicity including complete inhibition of spermatogenesis with the highest dose, evidence of arrested mitosis, signs of pyknosis, and no mature sperm. However, interstitial cells were unchanged, and fibrosis and inflammatory infiltrates were not observed. Nine weeks after the end of nifurtimox exposure, all testicular effects were almost entirely reversed.

In a male and female fertility study in rats, nifurtimox was administered in dietary feed at doses of 150 ppm (equivalent to 7-15 mg/kg), 300 ppm (equivalent to 15-30 mg/kg/day), and 600 ppm (equivalent to 30-60 mg/kg/day) for 10 weeks before mating. Male fertility was completely inhibited in rats administered 30-60 mg/kg/day nifurtimox, but female fertility was not affected for the same dosing regimen. In a recovery study, 11 weeks after the end of dosing, fertility was still inhibited in 75% of male rats administered nifurtimox for 32 weeks indicating a lack of complete reversibility. The nifurtimox dose in male rats that was not associated with inhibition of fertility was considered to be at <30 mg/kg/day which is approximately equivalent to 0.5 times the MRHD for fertile males.

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<sup>32</sup> Schmid C, Kuemmerle A, Blum J, et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for T. b. gambiense sleeping sickness. PLoS Negl Trop Dis. 2012;6:e1920.

The reader is referred to the Pharmacology/Toxicology review by James Wild, Ph.D., and Terry Miller, Ph.D, DARRTS.

#### Review of Literature

The applicant and DPMH conducted a review regarding nifurtimox exposure and females and males of reproductive potential, and no data were found.

*Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.*

### **DISCUSSION AND CONCLUSIONS**

#### Pregnancy

Nifurtimox crosses the placental barrier in animals and has been shown to have significant embryofetal toxicity in animals, including fetal malformations in rabbits (fusion of caudal vertebral bodies and ventricular septal defects) at doses 0.2 and 0.5, times respectively, the MRHD (see section above under Pregnancy-Nonclinical Experience for further details).

Limited data from a phase 3 clinical study of nifurtimox treatment for Chagas Disease in pregnancy in five subjects are insufficient to determine a drug-associated risk of miscarriage, major congenital anomalies or maternal or fetal adverse effects. Following discussions with the review division, DPMH has determined that (b) (4) due to the high degree of embryofetal toxicity seen in animal studies a Warning and Precaution for embryofetal toxicity should be added to the labeling.

Although the WHO recommends not treating CD with antiparasitic drugs during pregnancy, and the CDC recommends waiting until after pregnancy has ended to treat CD, there is still the possibility of unintended pregnancies in females of reproductive potential who are taking nifurtimox to treat chronic CD as indicated by the five pregnancies that occurred in the clinical trial and the fact that over 40,000 females of reproductive potential are infected with CD in the U.S alone. In addition, the WHO notes that a recent shift in approaches to prevent transmission globally is through active, systematic screening and treatment of females of reproductive potential to prevent transmission of Chagas disease throughout pregnancy and birth. Considering that nifurtimox has the potential for use among females of reproductive potential, gathering additional pregnancy exposure data is important to assess the safety of this drug during pregnancy. Lampit will be indicated for the treatment of Chagas disease caused by *Trypanosoma cruzi* (*T. cruzi*) in patients less 18 years of age; therefore, DPMH recommends issuing a postmarketing requirement (PMR) for a Single-Arm Pregnancy Safety Study. The reader is referred to the FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies: Considerations for Study Design, published May 2019, for further details.

### Lactation

Based on published literature, nifurtimox is present in human milk with estimated relative infant doses (RIDs) below 10%. Although one study<sup>19</sup> [Moroni et al. (2019)] notes that the M/P ratio was high, suggesting concentration of nifurtimox in human milk, overall, there have been no reports of any adverse outcomes in any of the small number of infants exposed to nifurtimox during lactation.

The DAI clinical pharmacology reviewer recommended that the inclusion of "...less than 15% of the recommended dose for pediatric Chagas patients..." is a reasonable conservative estimate for Chagas patients based on the information from the literature. Based on this opinion from clinical pharmacology, and that the estimated RIDs were less than 10%, and given the lack of adverse events seen in infants exposed via breast milk, DPMH recommends that the standard risk/benefit statement is used in subsection 8.2 of labeling:

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LAMPIT and any potential adverse effects on the breastfed infant from LAMPIT or from the underlying maternal condition.

In addition, DPMH recommends including information in subsection 8.2 of labeling about potential adverse effects that may be observed in the breastfed infant (ie. vomiting, rash, decreased appetite, pyrexia, and irritability).

In addition, since there are published studies that document the amount of nifurtimox in human milk, further evaluation with a postmarketing clinical lactation study is not needed at this time.

### Females and Males of Reproductive Potential

There are no human data available on the effect of nifurtimox on fertility. Based on animal fertility studies, nifurtimox may impair fertility in male patients. These effects persisted after discontinuing the drug in 75% of the animals effected. Therefore, subsection 8.3 will contain a section describing the potential for nifurtimox 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 also be added to subsection 8.3. Since the drug is genotoxic, based on the recommendations from the guidance published in 2019, *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry*<sup>33</sup>, females of reproductive potential should use contraception during treatment with Lampit and for 6 months after the last dose of Lampit. In addition, males with female partners will be advised to use condoms during treatment with Lampit and for 3 months after the last dose of Lampit.

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<sup>33</sup> Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry. May 2019. <https://www.fda.gov/media/124829/download>

## Postmarketing Requirement (PMR) Recommendations

DPMH recommends the following PMR is issued to the applicant:

1. Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to nifurtimox during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

## LABELING RECOMMENDATIONS

DPMH revised sections 2, 5, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

### DPMH Proposed Pregnancy and Lactation Labeling

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

##### -----DOSAGE AND ADMINISTRATION-----

- Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with LAMPIT (5.6, 8.1, 8.3).

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

- Potential for Genotoxicity and Carcinogenicity (5.7).
- Embryo-Fetal Toxicity: May 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 (2.3, 5.6, 8.1, 8.3)

## FULL PRESCRIBING INFORMATION

### 2 DOSAGE AND ADMINISTRATION

- Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with LAMPIT [see *Warnings and Precautions* (5.6), and *Use in Specific Populations* (8.1, 8.3)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.6 Embryo-Fetal Toxicity

Based on findings from animal studies, LAMPIT may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, nifurtimox administered orally to pregnant mice, rats, and rabbits during organogenesis was associated with reduced fetal body weights in rodents, and abortions, fetal death, and smaller litter sizes in rabbits at doses approximately equivalent to and 2-times respectively the maximum recommended human dose (MRHD) of 10 mg/kg/day. Fetal malformations were observed in pregnant rabbits administered nifurtimox in doses less than the MRHD [see *Use in Specific Populations* (8.1)]. Advise pregnant women of the potential risk to a fetus. Pregnancy testing is recommended for females of reproductive potential [see *Dosage and Administration* (2.3)]. Advise females of reproductive potential to use effective contraception during treatment with LAMPIT and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use condoms during

treatment and for 3 months after the last dose of LAMPIT [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on animal studies, LAMPIT Tablets may cause fetal harm when administered to a pregnant woman. Published postmarketing reports on nifurtimox use during pregnancy are insufficient to inform a drug-associated risk of birth defects and miscarriage. There are risks to the fetus associated with Chagas Disease (see *Clinical Considerations*).

Nifurtimox administered orally to pregnant mice, rats, and rabbits during organogenesis was associated with reduced fetal body weights in mice, reduced maternal and fetal body weights in rats, and abortions, reduced maternal weight gain, and reduced numbers of live fetuses in rabbits when nifurtimox was administered orally during organogenesis at doses approximately equal to the MRHD in rodents and 2-times the MRHD in rabbits. Increased incidences of fetal skeletal (fusion of caudal vertebral bodies), and visceral (ventricular septal defect of the heart) malformations occurred in rabbits at nifurtimox doses approximately 0.2 and 0.5 times respectively the MRHD. In a pre-postnatal study, maternal body weights and fetal body weights of first generation offspring were reduced at a doses approximately equal to or 0.5 times the MRHD respectively, and several male offspring in the nifurtimox treatment groups exhibited slightly small testes at doses  $\geq 0.2$  times the MRHD (see *Data*). Advise pregnant women of the potential risk to a fetus.

There is a pregnancy safety study for LAMPIT. If LAMPIT is administered during pregnancy, or if a patient becomes pregnant while receiving LAMPIT or within six months following the last dose of LAMPIT, healthcare providers should report LAMPIT exposure by calling xxx-xxx-xxxx.

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 Lampit.

Acute symptomatic Chagas disease is rare in pregnant women; however, symptoms may be serious or life-threatening. If a pregnant woman presents with acute symptomatic Chagas disease, the risks versus benefits of treatment with Lampit to the mother and the fetus should be evaluated on a case-by-case basis.

## Data

### *Animal Data*

In preliminary embryo-fetal studies, pregnant mice and rats were administered 20, 50, and 125 mg/kg/day nifurtimox during the period of organogenesis [gestation day (GD) 6 to GD 15 for both species]. Maternal body weights were significantly reduced in the 50 and 125 mg/kg/day dose groups in rats, but not in mice. No fetal malformations were reported for either species, but mean fetal weights were significantly reduced in the 125 mg/kg/day dose group in mice and in the 50 and 125 mg/kg/day dose groups in rats. No maternal toxicity was observed in mice at 125 mg/kg/day or in rats at 20 mg/kg/day (respectively approximately equal to or 0.3-times the MRHD based on body surface area comparison). No adverse fetal effects were observed in mice at a dose of 50 mg/kg/day or in rats at a dose of 20 mg/kg/day (respectively equivalent to 0.4-times or 0.3-times the MRHD based on body surface area comparison).

In pregnant rabbits administered 5, 15, and 60 mg/kg/day nifurtimox during the period of organogenesis (GD 6 to GD 20), the high dose was associated with maternal toxicity including reduced body weights and food consumption, and abortions in 8/20 high-dose dams. The mean number of live fetuses/litter and the percent of live fetuses per total implantations per group were significantly lower in the mid- and high-dose groups compared to the control group. Nifurtimox administration was associated with an increased fetal and litter incidences of skeletal (fusion of caudal vertebral bodies) and visceral (ventricular septal defect) malformations in fetuses in the low- and mid-dose groups receiving 5 and 15 mg/kg/day respectively (approximately equivalent to 0.2-times and 0.5-times the MRHD respectively based on body surface area comparison). No maternal toxicity was observed at 15 mg/kg/day which is approximately equivalent to 0.5 times the MHRD based on body surface area comparison.

In a pre-postnatal study, pregnant female rats were administered 15, 30, and 60 mg/kg/day nifurtimox during organogenesis and lactation [GD 6 to lactation day (LD) 21]. Maternal findings included reduced maternal body weights in high-dose dams during gestation and to a lesser degree during lactation. In first generation offspring, body weights were significantly reduced in males and females in the high-dose group during the lactation and post-lactation periods. Physical development, neurological function, and reproduction of first-generation offspring were not substantially changed in the nifurtimox treatment groups, but 5-20% of male offspring in all the nifurtimox treatment groups exhibited slightly small testes. No adverse maternal effects or fetal effects on first generation female offspring occurred at 30 mg/kg/day, and no adverse fetal effects on the development of male offspring occurred at 15 mg/kg/day (respectively approximately 0.5- and 0.2-times the MRHD based on body surface area comparison).



## 8.2 Lactation

### Risk Summary

Published literature demonstrates that nifurtimox is present in human breast milk with an estimated infant daily dose of less than 15% of the recommended daily dose for pediatric Chagas' patients. There were no reports of adverse effects on the small number of infants who were breastfed by mothers taking nifurtimox. There is no information on the effects of nifurtimox on milk production. Monitor infants exposed to LAMPIT through breast milk for vomiting, rash, decreased appetite, pyrexia, and irritability

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LAMPIT and any potential adverse effects on the breastfed infant from LAMPIT or from the underlying maternal condition.

## 8.3 Females and Males of Reproductive Potential

### Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential.

### Contraception

#### *Females*

LAMPIT tablets may 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 LAMPIT tablets and for 6 months after the final dose.

#### *Males*

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use condoms during treatment and for 3 months after the final dose of LAMPIT [*see Nonclinical Toxicology (13.1)*].

### Infertility

#### *Males*

Based on findings in rodents, LAMPIT may impair fertility in males of reproductive potential. These effects on fertility were not reversible in 75% of the animals at 11 weeks after dosing [*see Nonclinical Toxicology (13.1)*].

## 17 PATIENT COUNSELING INFORMATION

Embryo Fetal Toxicity [*see Warnings and Precautions (5.6) and Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)*].

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception while taking LAMPIT tablets and for 6 months after the last dose.
- Advise male patients with female partners of reproductive potential to use condoms during treatment and for 3 months after the final dose of LAMPIT.

### Lactation

Advise nursing mothers to monitor infants exposed to LAMPIT through breast milk for vomiting, rash, decreased appetite, fever, and irritability [*Use in Specific Populations (8.2)*].

### Infertility

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

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### Clinical Inspection Summary

Date	25 June 2020
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Gregory DiBernardo, RPM Mukil Natarajan, MD, Clinical Reviewer Peter Kim, MD, Clinical Team Lead Sumathi Nambiar, MD, Division Director, Division of Anti-Infective Products (DAI)
NDA #	213464
Applicant	Bayer Healthcare Pharmaceuticals, Inc
Drug	Lampit (nifurtimox)
NME	Yes
Proposed Indication	Treatment of Chagas' disease (American Trypanosomiasis) caused by <i>Trypanosoma cruzi</i> ( <i>T. cruzi</i> )
Consultation Request	15 January 2020
Summary Goal Date	10 July 2020
Action Goal Date	6 August 2020
PDUFA Date	6 August 2020

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections of the clinical sites of Drs. Sierra and Ramirez, covering Protocol 16027 (Part 1), were conducted in support of this NDA. In addition, an investigation that entailed a review of the primary efficacy endpoint data for Protocol 16027 (Part 1) for these two sites was conducted at the sponsor, Bayer Healthcare Pharmaceuticals, Inc. Overall, the study appears to have been conducted adequately, and the primary efficacy endpoint data generated by these sites appear acceptable in support of the respective indication.

Of note, the final reports have not yet been received from ORA for the inspection of Dr. Ramirez and for the investigation of the primary efficacy endpoint data for both sites at the sponsor. Therefore, this Clinical Inspection Summary is based in part on communications with the ORA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of these reports.

## II. BACKGROUND

This application was submitted in support of the use of Lampit (nifurtimox) for the treatment of Chagas' disease (American Trypanosomiasis) caused by *Trypanosoma cruzi* (*T. cruzi*) in children younger than 18 years of age. The key study supporting the application was the following:

- Protocol #16027, "Prospective, historically controlled study to evaluate the efficacy and safety of a new pediatric formulation of nifurtimox in children aged 0 to 17 years with Chagas' disease"

### Protocol 16027

- *Subjects*: 371 subjects were screened; 330 subjects were randomized and received at least 1 dose of study drug
- *Sites*: 25 sites in Argentina (18 sites), Bolivia (3 sites), and Colombia (4 sites)
- *Study Initiation and Completion Dates*: 27 Jan 2016 (first patient, first visit) to Completion of Part 1 on 25 Jul 2018 (last patient, last visit)
- *Database Lock*: 14 September 2018

This was a prospective, historically-controlled, randomized, age-stratified, double-blind, parallel-group study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of oral administration of nifurtimox in children with a diagnosis of Chagas' disease. The study consisted of two parts:

- Part 1 (CHICO) comprised the treatment with nifurtimox including the 1-year follow up. This portion was designed to develop a better understanding of the efficacy, safety, tolerability, and PK of nifurtimox in children with a diagnosis of Chagas disease using pediatric formulations.
- Part 2 (CHICO SECURE), the 3-year long-term follow-up, assesses the incidence of seronegative conversion in subjects who were randomized and received at least one dose of their assigned 60- or 30-day nifurtimox treatment regimen. This portion of the study was designed as a post marketing commitment at the request of the FDA. The study results for Part 2 are pending.

The primary objective of Part 1 was to assess the superiority of a 60-day regimen of nifurtimox to historical untreated control at the 12-month follow-up (360 days from end of treatment [EOT]) as either:

- Sero-reduction (defined as a  $\geq 20\%$  reduction in optical density measured by conventional enzyme-linked immunosorbent assays [ELISAs]) compared to baseline in subjects  $\geq 8$  months to  $< 18$  years of age at randomization; or
- Sero-conversion (defined as negative Immunoglobulin G [IgG] concentration in all subjects)

Eligible subjects were stratified by age (into four strata: 0 to 27 days of age, 28 days to younger than 8 months of age, 8 months to younger than 2 years of age, and 2 years to younger than 18 years of age) and randomized on Visit 2 (Day 1) via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 2:1 ratio to one of two treatment groups as follows:

- Treatment Group 1 (60-day regimen): Nifurtimox tablets administered three times daily for 60 days
- Treatment Group 2 (30-day regimen): Nifurtimox tablets administered three times daily for 30 days, followed by nifurtimox placebo administered three times daily for 30 days

The study drug was supplied as follows:

- Nifurtimox 30 mg oral tablets
- Nifurtimox 120 mg oral tablets
- Matching placebo tablets for each dosage strength

The total daily dose administered for infants and children weighing more than 6.0 kg and <40 kg was 10-20 mg/kg. Total daily dosage for adolescents weighing 40 kg or greater was 8-10 mg/kg.

At Visit 2, study drug and subject compliance diaries were dispensed and instructions for study drug administration and completion of diaries were provided to all subjects. Subjects returned for efficacy and safety assessments at Visits 3, 6, and 8 (the end-of-treatment [EOT] visit). For Visits 4, 5, and 7, subjects were contacted via telephone for to assess for occurrence of AEs, use of concomitant medications, compliance with study drug administration, and completion of subject diary or PK subject diary.

At Visit 6 (Day 30), subjects returned all remaining study drug and empty packaging, and study drug for the remaining 30 days of treatment, along with subject compliance diaries were dispensed. After the EOT visit (Visit 8), subjects returned to the site on Days 90 (Visit 9), Day 240 (Visit 10), and Day 420 (Visit 11) for additional efficacy and safety assessments. The total duration of each subject's participation was approximately 14 months.

The *primary efficacy endpoint* was sero-reduction or sero-conversion using two conventional ELISA serology tests in the nifurtimox 60-day regimen at 12 months post-treatment (Visit 11).

- Sero-reduction was defined as a  $\geq 20\%$  reduction in optical density in subjects  $\geq 8$  months to <18 years of age at randomization
- Sero-conversion was defined as negative IgG concentration in all subjects; both conventional ELISA serology test results should have been negative for the subject to be considered as seroconverted.

Sero-reduction or sero-conversion was considered a cure, and the primary variable was binary (cure, no cure). For primary efficacy endpoint assessment, site personnel collected and sent serology test samples to a central laboratory ( (b) (4) ), located in

(b) (4). The central laboratory processed the samples once all samples for an individual patient were available.

#### Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history.

### III. RESULTS (by site):

1. Victor Sierra, MD  
Site #48001  
Calle 17 No. 26 05 barrio Los Helechos  
Yopal, Casanare 850001  
Colombia  
Inspection Dates: 24 to 28 February 2020

Because of FDA restrictions on conducting inspections in Colombia, South America, Dr. Sierra authorized the inspection to be conducted remotely at Bayer Healthcare Pharmaceuticals in New Jersey. Bayer subsequently obtained certified copies of the original paper medical records and other source documents for all subjects screened and enrolled at this site. These records were uploaded to a virtual cloud service provider and provided to FDA through a secure file share system. A translator, provided by the sponsor, was present during the inspection.

At this site for Protocol 16027, 78 subjects were screened and 67 were enrolled. Per the sponsor's data listings, 65 subjects completed the study; two subjects withdrew due to adverse events (i.e., rash in Subject # (b) (6) and seizure in Subject # (b) (6)). Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee submissions and approvals, informed consent, subject eligibility criteria, randomization procedures, source data and records, electronic case report forms, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for 21 of the 78 subjects who were screened was conducted. There was no evidence of under-reporting of adverse events, and no GCP compliance issues were noted.

2. Teresa Ramirez, MD  
Site #43005  
Av Belgrano Norte 660  
Santiago del Estero, Santiago del Estero G4202AAT  
Argentina  
Inspection Dates: 8 to 11 June 2020

Because of travel restrictions in Argentina due to the ongoing COVID-19 pandemic, Dr.

Ramirez authorized the inspection to be conducted remotely at Bayer Healthcare Pharmaceuticals in New Jersey. Bayer subsequently obtained certified copies of the original paper medical records and other source documents for all subjects screened and enrolled at this site. These records were uploaded to a virtual cloud service provider and provided to FDA through a secure file share system. A translator, provided by the sponsor, was present during the inspection. Of note, the final report for this inspection of Dr. Ramirez has not yet been received from ORA. Therefore, this inspection summary is based on communication with the ORA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final inspection report.

At this site for Protocol 16027, 59 subjects were screened, 47 were enrolled, and 44 completed the study. Per the sponsor's data listings, 3 subjects withdrew due to noncompliance with the study drug (Subject (b) (6)), withdrawal by subject (Subject (b) (6)), and an adverse event (i.e., epigastric pain in Subject (b) (6)). Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee submissions and approvals, informed consent, subject eligibility criteria, randomization procedures, source data and records, electronic case report forms, adverse event reporting, protocol deviations, and monitor logs and follow-up letters.

An audit of the study records for 34 of the 47 subjects who were enrolled was conducted. According to the FDA field investigator, there was no evidence of under-reporting of adverse events, data integrity issues, or any other GCP compliance issues.

3. Bayer Healthcare Pharmaceuticals, Inc.  
P.O. Box 915  
100 Bayer Blvd.  
Whippany, NJ 07981-0915  
Investigation Dates: 1 to 5 June 2020

An investigation of the sponsor was conducted that entailed a review of the source records for the qualitative and quantitative serology testing results from the (b) (4) located in (b) (4). Of note, the final report for this audit of the primary efficacy endpoint data has not yet been received from ORA. Therefore, this summary is based on communication with the ORA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final inspection report.

According to the FDA field investigator, certified copies of the source records for the recombinant ELISA and Total Purified Antigen serology tests were reviewed and verified against the data listings provided by the sponsor for all 67 subjects who were randomized at Dr. Sierra's site (Site 48001) and all 47 subjects who were randomized at Dr. Teresa Ramirez's site (Site 43005). No issues or discrepancies were noted.



The FDA field investigator further noted that Bayer was unable to provide certified copies of the source records for the following serology test results.

- qPCR
- Indirect Hemagglutination (IHA)
- Non-conventional test

The qPCR, IHA, and non-conventional serology test results were reviewed and verified against screen shots of the data that had been transcribed into an electronic database from paper source records. While no discrepancies were noted by the FDA field investigator when comparing the screen shots of the electronic data (that also included screen shots of the audit trail information) with the sponsor data listings, we are unable to determine if any discrepancies occurred between the original paper source records and the sponsor's data listings submitted to the NDA for the qPCR, Indirect Hemagglutination Assay, and the non-conventional test.

{See appended electronic signature page}

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Central Doc. Rm. NDA 213464

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DNP/Clinical Team Leader/ Peter Kim

DNP/Division Director/ Sumathi Nambiar

OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/Phillip Kronstein

OSI/DCCE/GCP Reviewer/Cheryl Grandinetti

OSI/ GCP Program Analysts/Yolanda Patague

OSI/Database Project Manager/Dana Walters

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/s/  
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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)

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Date of This Memorandum:	May 19, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213464
Product Name and Strength:	Lampit (nifurtimox) Tablets, 30 mg and 120 mg
Applicant/Sponsor Name:	Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
OSE RCM #:	2019-2503-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 15, 2020 for Lampit. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for Lampit (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.<sup>a</sup>

## 2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

**3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page**

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<sup>a</sup> Myers D. Label and Labeling Review for Lampit (NDA 213464). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 14. RCM No.: 2019-2503.

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## Interdisciplinary Review Team for Cardiac Safety Studies

### QT Study Review

Submission	NDA 213464
Submission Number	027
Submission Date	4/7/2020
Date Consult Received	4/7/2020
Drug Name	LAMPIT (nifurtimox), Tablet
Indication	Treatment of Chagas' disease (American Trypanosomiasis) caused by <i>Trypanosoma cruzi</i> (T. cruzi)
Therapeutic dose	Body weight based dose up to 300 mg three times a day (TID)
Clinical Division	DAI

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous QT-IRT review under IND 109901 dated 01/07/2013 in DARRTS;
- Previous QT-IRT review under NDA 213464 dated 03/02/2020 in DARRTS;
- Study 16027 [report](#) and [additional tables/figures](#) (Submission 0001);
- Proposed [label](#) (Submission 0001);
- Sponsor's response to IR requests in submissions [0009](#), [0010](#), [0013](#);
- [Investigator's brochure](#) (Submission 0004);
- Highlights of clinical pharmacology and cardiac safety ([link](#)).

## 1 SUMMARY

No large QTc prolongation effect (>20 msec) of nifurtimox was observed in this QT assessment. Without a positive control or large exposure margin, we are reluctant to draw conclusions of lack of an effect (ICH E14 Q&A (R3) 6.1).

The effect of nifurtimox was evaluated in Phase 3 study 16027. The highest dose evaluated was the proposed body weight/age-based dose administered TID with food for 60 days. Data from 5 clinical sites with automatic ECG measurements were evaluated using central tendency by-time analysis as the primary analysis, which did not suggest that nifurtimox was associated with large mean increases in the QTc interval (refer to section 4.3) – see Table 1 for overall results. The data did not support an exposure-response analysis. Subjects with QTc >480 msec and/or with a change from baseline QTc >60 msec occurred on-treatment and off-treatment during the placebo or follow-up period where no study drug was administered. Therefore, these outlier values may not be drug-related.

**Table 1: The Point Estimates and the 90% CIs  
(FDA Analysis, On-Treatment Data\*)**

ECG parameter	Treatment	N	Day	Time (hours)	$\Delta$ QTcF (msec)	90.0% CI (msec)
QTc	Nifurtimox TID x 30 days	34	30	2	5.3	(0.4, 10.3)
QTc	Nifurtimox TID x 60 days	72	60	2	4.8	(1.4 , 8.2)

\*  $\leq 30$  days for Nifurtimox TID x 30 days and  $\leq 60$  days for Nifurtimox TID x 60 days.

The sponsor has not conducted organ impairment studies or drug-drug interaction studies in this pediatric development program. Nifurtimox is not a P-gp- or BCRP substrate, urine recovery is not significant, and there is no participation of typical liver enzymes in nifurtimox metabolic turnover.

### 1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

### 1.2 COMMENTS TO THE REVIEW DIVISION

The ECG quality in Study 16027 is suboptimal because only paper ECGs were collected, ECG data were manually evaluated by the investigators at the local study sites, and most of the paper ECGs did not come with automatic measurements from the ECG device. In addition, the study design did not include placebo or positive controls or have a large exposure margin. Therefore, the data are not adequate to exclude a 10-msec mean increase in QTc, i.e., the regulatory threshold in ICH E14 guideline.

## 2 RECOMMENDATIONS

### 2.1 ADDITIONAL STUDIES

A thorough QT study could be conducted as a PMR if the Division considers it necessary to know whether nifurtimox prolongs the QTc  $\geq 10$  msec as per ICH E14 guideline.

### 2.2 PROPOSED LABEL

The sponsor did not propose QT labeling language in Section 12.2 in the label submitted to Submission 0001 ([link](#)). We propose the following language for the Division to consider.

#### **12.2 Pharmacodynamics**

##### Cardiac Electrophysiology

At the recommended dose, nifurtimox treatment does not result in large mean increases ( $>20$  ms) in the QTc interval.

*The data from study 16021 are not adequate to support an exclusion of small mean increases (10 msec) in the QTc interval as per ICH E14.*

### 3 SPONSOR'S SUBMISSION

#### 3.1 OVERVIEW

##### 3.1.1 Clinical

LAMPIT (nifurtimox) is an antiprotozoal, indicated in term newborns, infants, children and adolescents less than 18 years of age for the treatment of Chagas disease (American Trypanosomiasis) caused by *Trypanosoma cruzi* (*T. cruzi*). The proposed therapeutic dose is oral tablet with food, 3 times daily for 60 days. The total daily dose is body weight based as shown in the table below:

Body weight group	Total daily dose of nifurtimox [mg/kg body weight]
(b) (4) ( $\geq 40$ kg) <sup>a</sup>	8–10
(b) (4) (<40 kg)	10–20
(b) (4) <sup>b</sup> Term newborn with body weight of $\geq 2,500$ g	

The sponsor is submitting a QT assessment using PK/ECG data from Phase 3 study 16027 to support an accelerated approval of LAMPIT. Study 16027 is a prospective, historically controlled study to evaluate the efficacy and safety of a pediatric formulation of nifurtimox in children aged 0 to 17 years with Chagas' disease. Approximately 300 pediatric subjects with Chagas disease were stratified into 4 age groups (Stratum 1: 0-27 days; Stratum 2: 28 days to <8 months; Stratum 3: 8 months to <2 years; Stratum 4: 2 years to <18 years). Within each group, patients were randomized to receive nifurtimox either as a 60-day regimen (n = 200) or a 30-day regimen (n = 100; 30-day treatment with nifurtimox followed by 30-day treatment with placebo). Changes in QT/QTc interval were evaluated in ECGs obtained at screening, during the treatment period at 2-4 hours postdose at Visits 2 (Day 1), 3 (Day 7 $\pm$ 1), 6 (Day 30 $\pm$ 3) and 8 (Day 60 $\pm$ 3), and during the follow-up period at Visits 9 (Day 90 $\pm$ 7), 10 (Day 240 $\pm$ 7) and 11 (Day 420 $\pm$ 7). 12-lead ECG was optional in subjects <5 years of age at the discretion of the investigator. Blood samples for pharmacokinetic parameters were obtained prior to administration of study drug, and at 2-4 hours postdose at Visits 2, 3, 6 and 8. PK sampling was optional. The sponsor provided summary statistics and conducted outlier analysis on ECG parameters, and conducted exploratory analysis on the relationship between QTcB/QTcF and nifurtimox plasma concentration.

The reviewer conducted by-time analysis and concentration-QTc analysis using automatic measurements from 5 sites and conducted categorical analysis using all available ECG data.

##### 3.1.2 Nonclinical Safety Pharmacology Assessments

In vitro (GLP), exposure of HEK293 cells stably transfected with the hERG K<sup>+</sup> channel to nifurtimox was associated with concentration-dependent inhibition of the hERG-mediated tail current amplitude. The effect of nifurtimox reached threshold (IC<sub>20</sub>) and half-maximal inhibitory concentrations (IC<sub>50</sub>) at approximately 13  $\mu$ mol/L and 98  $\mu$ mol/L (extrapolated), respectively.



Refer to Highlights of Clinical Pharmacology and Cardiac Safety ([link](#)) for preclinical cardiac safety data from other in vitro/in vivo studies.

**Reviewer's Comment:** *In the Phase 3 study, the maximum geometric mean  $C_{max,ss}$  value across different age groups is 465 ng/mL. The ratio  $IC_{50}$  (extrapolated) and free  $C_{max,ss}$  is 165-fold.*

## 3.2 SPONSOR'S RESULTS

### 3.2.1 By-Time Analysis

Nifurtimox excluded the 20 ms threshold at the dose of 300 mg TID.

The sponsor performed mean change from baseline by visit in QTcF using full analysis data set. There were 330 subjects (111 subjects in 30-day and 219 subjects in 60-day regimens). The sponsor presented summary statistics such as mean, SD, minimum, median and maximum without confidence intervals. Please see study 16027, Table 14.3.5/ 11, page 581/1107 ([report](#)).

**Reviewer's comment:** *The reviewers used the data from 5 sites where automatic measurements were evaluated using central tendency by-time and by-day analysis. There were 106 subjects (34 subjects in 30-day and 72 subjects in 60-day regimens) in the 5 sites with automatic measurements. Please see section 4.3 for additional details.*

#### 3.2.1.1 Assay Sensitivity

Not applicable.

##### 3.2.1.1.1 QT Bias Assessment

Not applicable.

### 3.2.2 Categorical Analysis

The sponsor performed categorical analysis on QTcF by visit using full analysis data set (102 subjects in 30-day and 199 subjects in 60-day regimens). Please see study 16027, Table 10-19 ([report](#)).

The reviewer performed categorical analysis using data only from the treatment period. One subject had QTcF >480 msec but <500 msec in the 60-day regimen. Four subjects in a 30-day regimen and six subjects in a 60-day regimen had  $\Delta QTcF$  >60 msec. See section 4.4 for additional details.

### 3.2.3 Exposure-Response Analysis

The sponsor did not conduct a formal exposure-response analysis. The sponsor conducted linear regression on QTc and QTc change from baseline versus nifurtimox plasma concentration at 2-4 hours postdose. The sponsor's exploratory analysis does not suggest a trend for positive exposure-response relationship between  $\Delta QTcF$  and nifurtimox plasma concentration.

**Reviewer's comment:** *PK/ECG sampling schedule in study 16027 is too sparse to support a formal concentration-QTc analysis for a quantitative estimate on the QT*

*prolonging effect of nifurtimox. The results of the reviewer's graphical analysis are similar to the sponsor's results.*

### 3.2.4 Cardiac Safety Analysis

One subject died due to a post-treatment SAE (complete suicide) that occurred approximately 11 months after the end of treatment with study drug.

Serious AEs were reported for a total of 17 (5.2%) subjects (60-day: 5.5%, 30-day: 4.5%). None of the AEs were cardiac; however, two subjects reported seizures and 1 subject reported syncope.

- Subject (b) (6) (12 y/o female) presented with fever and two episodes of generalized tonic clonic seizures (MedDRA PT: Febrile convulsion) lasting for 2 min and 3-4 min, respectively on (b) (6) (11 days after starting the study drug); she was hospitalized after consultation in the emergency room. The study drug was interrupted on (b) (6) due to both the serious events. The subject received remedial drug therapy that included Dipyron (metamizole sodium) for complex febrile seizure, and clarithromycin and penicillin for pneumonia. The subject also received omeprazole for gastric protection. The event complex febrile seizure resolved on (b) (6). On (b) (6), the study drug was restarted and the subject was discharged without medication. ECG obtained on (b) (6) showed normal ventricular rate and no QTc prolongation.
- Subject (b) (6) (10 y/o female) was hospitalized due to seizure (MedDRA PT: seizure), which was of moderate intensity on (b) (6) (9 days after starting the study drug). The event was treated with remedial drug therapy that included Metoclopramide (metoclopramide), Saline solution (sodium chloride), and ranitidine. The event resolved on (b) (6), and the subject was discharged from the hospital on the same day. On (b) (6) (31 days after starting the study drug), the subject was hospitalized due to a second episode of seizure (MedDRA PT: seizure), which was of moderate intensity. The event was considered serious as it led to hospitalization. A CT scan performed on the same day was found to be normal. The subject's family history included seizures. The study drug was withdrawn due to the event. The event resolved on (b) (6), and the subject was discharged home on the same day with anticonvulsive medication. The investigator assessed both episodes of seizure as related to the study drug, but unrelated to the protocol-required procedures, citing the concomitant medication Marcol (dimenhydrinate) (self-medication leading to drug intoxication) as an alternative possible explanation. The event coincided with a drug intoxication due to self-medication with dimenhydrinate for which seizure is a known complication. The Sponsor assessed both episodes of seizure as unrelated to the study drug. The subject could not complete the study treatment due to the adverse event seizure (onset date: (b) (6)) and received the last dose of the study drug on (b) (6). The EOT visit (Visit 8) was performed on (b) (6). ECGs for this subject were normal and no evidence of QTc prolongation.
- Subject (b) (6) (11 y/o male) inadvertently tangled his neck in a rope while playing and experienced syncope of mild intensity. The subject's parents promptly untangled the rope, and the subject recovered from unconsciousness

immediately. The subject was hospitalized for observation on the same day (b) (6)  
The event was considered serious as it required hospitalization.

A total of 14 (4.2%) subjects discontinued study drug due to an AE. In total, 3 (0.9%) subjects reported drug-related SAEs leading to discontinuation of study drug. There were no cardiac-related AEs leading to discontinuation.

No TEAE of 'Electrocardiogram QT prolonged' was reported in any subject.

An increase in QTcF was observed not only after administration of both nifurtimox and placebo, but also during the follow-up period where no study drug was administered. Changes in QT/QTc interval did not result in discontinuation of study drug in any subject. No cases of QTc interval prolongation-related morbidity were observed.

**Reviewer's comment:** *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

## 4 REVIEWERS' ASSESSMENT

### 4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor reported analysis results using QTcB and QTcF. The reviewers used QTcF for the primary analysis as no large increases or decreases in heart rate (i.e.  $|\text{mean}| < 10$  bpm) were observed (see section 4.3.2).

### 4.2 ECG ASSESSMENTS

#### 4.2.1 Overall

Paper ECGs were collected at all study sites. We limited the primary analysis to ECGs that were collected at the 5 sites with automatic readings in 106 subjects.

#### 4.2.2 QT Bias Assessment

Not applicable.

### 4.3 BY-TIME ANALYSIS

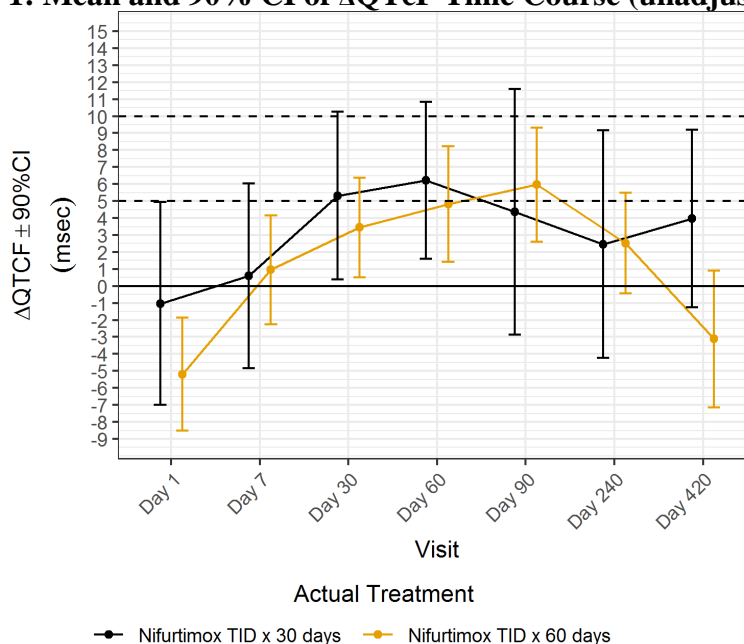
There were 106 subjects (34 subjects in 30-day and 72 subjects in 60-day regimens) in 5 clinical sites with automatic measurements.

All figures present days at 1, 7, 30, 60, 90, 240 and 420 for a 30-day and a 60-day regimens. **Study Days 90, 240 and 420 represented follow-up period where no study drug or placebo was administered.**

#### 4.3.1 QTc

Figure 1 displays the time profile of  $\Delta\text{QTcF}$  for nifurtimox three times daily. The largest upper bounds of the 2-sided 90% on the  $\Delta\text{QTcF}$  on-treatment ( $\leq 30$  days for the 30-day regimen and  $\leq 60$  days for the 60-day regimen) is shown in Table 1.

**Figure 1: Mean and 90% CI of  $\Delta$ QTcF Time Course (unadjusted CIs)**



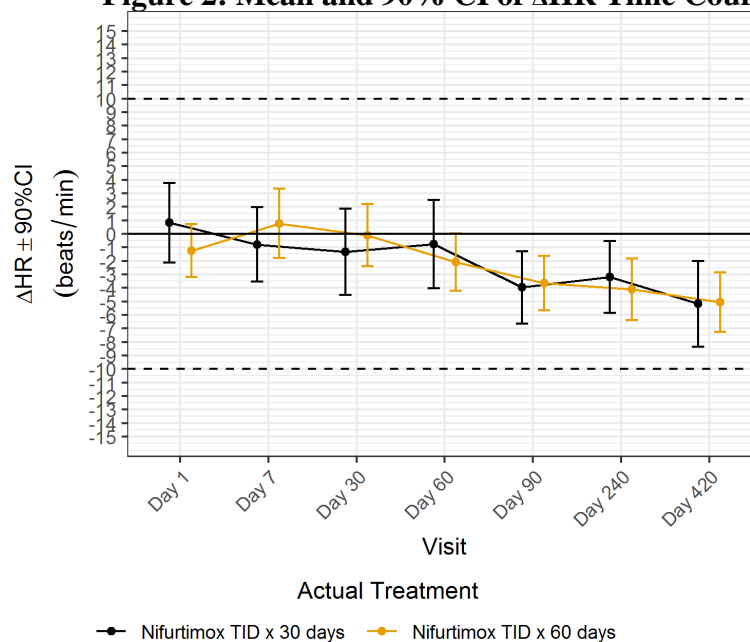
#### 4.3.1.1 Assay sensitivity

Not applicable.

#### 4.3.2 HR

Figure 2 displays the time profile of  $\Delta$ HR for nifurtimox three times daily.

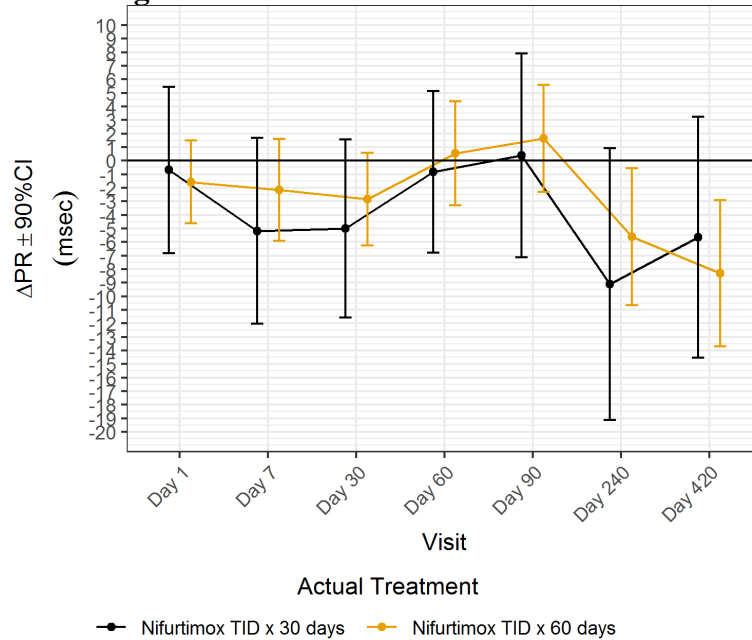
**Figure 2: Mean and 90% CI of  $\Delta$ HR Time Course**



#### 4.3.3 PR

Figure 3 displays the time profile of  $\Delta$ PR for nifurtimox three times daily.

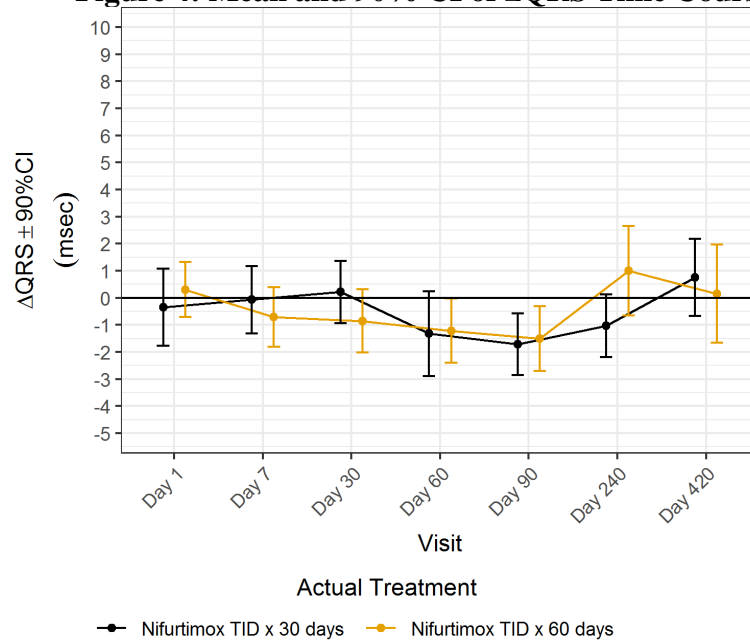
**Figure 3: Mean and 90% CI of  $\Delta$ PR Time Course**



#### 4.3.4 QRS

Figure 4 displays the time profile of  $\Delta$ QRS for nifurtimox three times daily.

**Figure 4: Mean and 90% CI of  $\Delta$ QRS Time Course**



#### 4.4 CATEGORICAL ANALYSIS

Categorical analysis were performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population (all clinical sites) and included on treatment data

collected  $\leq 30$  days for the 30-day treatment group and  $\leq 60$  days for the 60-day treatment group.

#### 4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTcF  $\leq 450$  msec, between 450 and 480 msec and between 480 and 500 msec. One subject had QTcF  $> 480$  msec in a Nifurtimox TID x 60 days.

**Table 2: Categorical Analysis for QTcF (On-Treatment Data\*)**

Actual Treatment	Total (N)		Value $\leq 450$ msec		450 msec < Value $\leq 480$ msec		480 msec < Value $\leq 500$ msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Nifurtimox TID x 30 days*	85	237	84 (98.8%)	236 (99.6%)	1 (1.2%)	1 (0.4%)	0 (0%)	0 (0%)
Nifurtimox TID x 60 days	178	665	171 (96.1%)	655 (98.5%)	6 (3.4%)	9 (1.4%)	1 (0.6%)	1 (0.2%)

\*  $\leq 30$  days for Nifurtimox TID x 30 days and  $\leq 60$  days for Nifurtimox TID x 60 days

During the follow-up period, one subject had QTcF  $> 500$  msec (change from baseline +102 msec) on study day 240.

Table 3 lists the categorical analysis results for  $\Delta$ QTcF ( $\leq 30$  msec, between 30 and 60 msec and  $> 60$  msec). Ten subjects, 4 subjects in the 30-day regimen and 6 subjects in the 60-day regimen, had  $\Delta$ QTcF  $> 60$  msec.

**Table 3: Categorical Analysis for  $\Delta$ QTcF (On-Treatment Data\*)**

Actual Treatment	Total (N)		Value $\leq 30$ msec		30 msec < Value $\leq 60$ msec		Value $> 60$ msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Nifurtimox TID x 30 days*	85	237	69 (81.2%)	213 (89.9%)	12 (14.1%)	16 (6.8%)	4 (4.7%)	8 (3.4%)
Nifurtimox TID x 60 days	178	665	142 (79.8%)	613 (92.2%)	30 (16.9%)	44 (6.6%)	6 (3.4%)	8 (1.2%)

\*  $\leq 30$  days for Nifurtimox TID x 30 days and  $\leq 60$  days for Nifurtimox TID x 60 days

In the Nifurtimox TID x 30 day treatment group, 2 subjects had  $\Delta$ QTcF  $> 60$  msec when taking placebo on Day 60. During the follow-up period where no study drug was administered, 7 subjects had an increase in baseline QTc  $> 60$  msec.

#### 4.4.2 HR

Table 4 lists the categorical analysis results for HR ( $\leq 100$  beat/min and  $> 100$  beat/min). Twenty-two subjects had HR  $> 100$  beats/min.

**Table 4: Categorical Analysis for HR (On-Treatment Data\*)**

Treatment Group	Total (N)		Value $\leq 100$ beat/min		Value $> 100$ beat/min & $\leq 25\%$	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Nifurtimox TID x 30 days*	85	237	78 (91.8%)	227 (95.8%)	7 (8.2%)	10 (4.2%)
Nifurtimox TID x 60 days	178	666	163 (91.6%)	632 (94.9%)	15 (8.4%)	34 (5.1%)

\*  $\leq 30$  days for Nifurtimox TID x 30 days and  $\leq 60$  days for Nifurtimox TID x 60 days

#### 4.4.3 PR

No subjects had PR >220 msec.

#### 4.4.4 QRS

Table 5 lists the categorical analysis results for QRS ( $\leq 120$  msec, and  $> 120$  msec with or without a 25% increase over baseline). One subject had QRS  $> 120$  msec with a 25% increase over baseline.

**Table 5: Categorical Analysis for QRS (On-Treatment Data\*)**

Actual Treatment	Total (N)		Value $\leq 120$ msec		Value $> 120$ msec & $\leq 25\%$		Value $> 120$ msec & $> 25\%$	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Subj.	# Obs.	# Subj.
Nifurtimox TID x 30 days	85	237	85 (100.0%)	237 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nifurtimox TID x 60 days	178	665	176 (98.9%)	663 (99.7%)	1 (0.6%)	1 (0.2%)	1 (0.6%)	1 (0.2%)

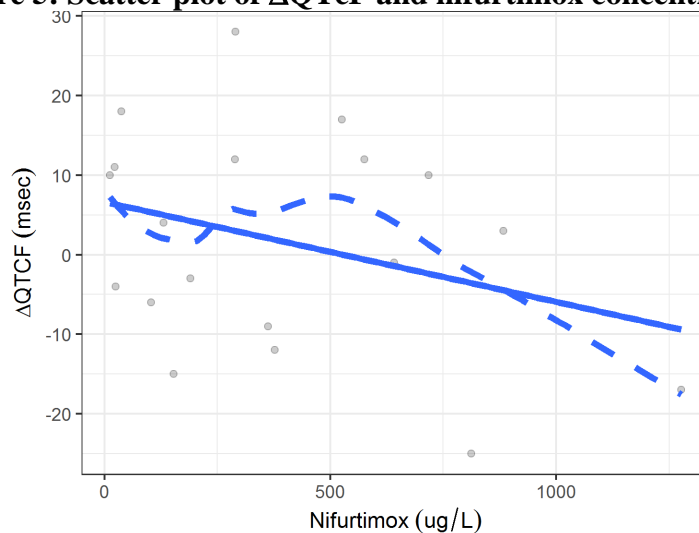
\*  $\leq 30$  days for Nifurtimox TID x 30 days and  $\leq 60$  days for Nifurtimox TID x 60 days

#### 4.5 EXPOSURE-RESPONSE ANALYSIS

The reviewer did not conduct a formal concentration-QTc analysis because the PK/ECG sampling schedule is too sparse to support an evaluation of model assumptions, especially the use of a direct effect model in the absence of significant hysteresis.

The reviewer conducted graphic analysis using PK/ECG data from the 19 subjects whose ECG data were derived from automatic machine reading. These subjects (5 from 30-day treatment arm and 14 from 60-day treatment arm) contributed 19 time-matched PK/ECG data in Visit 6 or 8. The scatter plot of  $\Delta QTcF$  vs concentration does not suggest a trend of increasing  $\Delta QTcF$  with higher drug exposure (Figure 5).

**Figure 5: Scatter plot of  $\Delta QTcF$  and nifurtimox concentration.**



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LARS JOHANNESSEN  
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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\*\*\*

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Date of This Review:	April 14, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213464
Product Name and Strength:	Lampit (nifurtimox) Tablets, 30 mg and 120 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
FDA Received Date:	December 6, 2019 and February 27, 2020
OSE RCM #:	2019-2503
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

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## 1 REASON FOR REVIEW

As part of the approval process for Lampit (nifurtimox) Tablets, the Division of Anti-Infectives (DAI) requested that we review the proposed Lampit prescribing information (PI) container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 REGULATORY HISTORY

On December 6, 2019, an original New Drug Application for Lampit (nifurtimox) Tablets, 30 mg and 120 mg was submitted, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

On February 27, 2020, Bayer provided their response to the Agency's Information Request (IR) dated February 13, 2020 which requested further information and clarity on Chemistry, Manufacturing and Controls (CMC) issues. Bayer, in addition to their responses to our IR<sup>a</sup>, submitted revised prescribing information (in both clean and tracked changes format), container labels, and carton labeling, incorporating updates to address the CMC issues.

## 3 MATERIALS 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

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

## 4 FINDINGS AND RECOMMENDATIONS

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<sup>a</sup> Cover Letter: Bayer's Response to FDA Request for Information (nifurtimox NDA 213464). Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2020 FEB 27. Available from: [\\cdsesub1\evsprod\nda213464\0016\m1\us\12-cover-letters\bayers-response-to-fda-request-for-information.pdf](#)

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the proposed Prescribing Information (PI) includes in Section 2.2, important instructions related to the preparation and administration of the proposed product. Additionally, the PI includes “Patient Information”, however lacks “Instructions for Use (IFU).”	For drug products that have “complicated or detailed patient-use instructions”, IFUs “help ensure that patients receive clear, concise information that is easily understood for the safe and effective use of prescription products” <sup>b</sup> . The proposed PI includes important information related to the preparation and administration of Lampit. Specifically, Section 2. (b) (4) includes information related to splitting tablets, preparing a slurry, and administering the product. However, the patient and/or caregiver does not normally have access to the	The Applicant needs to add an IFU that includes step by step instructions on how to split tablets, preparation of a slurry, and administer the product, along with visuals to help the patients understand the instructions <sup>c</sup> .

<sup>b</sup> Guidance for Industry: Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format (lines 17-24). Food and Drug Administration. 2019. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/instructions-use-patient-labeling-human-prescription-drug-and-biological-products-and-drug-device>.

<sup>c</sup> Guidance for Industry: Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format (lines 529-567). Food and Drug Administration. 2019. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/instructions-use-patient-labeling-human-prescription-drug-and-biological-products-and-drug-device>.

		important information regarding the appropriate dose preparation and administration in the PI. Lack of communicating the proper dose preparation and administration could result in wrong technique medication errors.	
Highlights of Prescribing Information			
1.	As currently presented under the "Dosage and Administration" header, the "total daily dose" is stated as "8-10 mg/kg" and "10-20 mg/kg."	The lower total daily dosage may be overlooked because it does not include the appropriate unit of measure (mg/mL). In addition, when a hyphen is included in a range instead of the word "to", the hyphen can be overlooked. For example, "8-10" could be misinterpreted as "810".	To provide clarity and minimize the risk of misinterpretation, add the unit of measure, "mg/kg" after the first Arabic numerals in the "total daily dose" ranges (i.e., "8" and "10"). We also recommend replacing the hyphens with their intended meaning "to."  For example, "8 mg/kg to 10 mg/kg" and "10 mg/kg to 20 mg/kg".
2.	As currently presented, the second bullet under the "Dosage and Administration" header states, (b) (4) ≥40Kg:..." is confusing and includes the symbols "<" and "≥". .	The symbols '<', '≤', '>', and '≥' are error-prone <sup>d</sup> because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration sections of the Highlights and Full Prescribing Information, could lead to medication errors.	To provide clarity we recommend revising (b) (4) ≥40Kg:..." to (b) (4) 40 kg or greater):..."

<sup>d</sup> ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2020 APR 03]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

3.	As currently presented, the third bullet under the "Dosage and Administration" header states, (b) (4) (b) (4) <40 kg:..." is confusing and includes the symbols "<".	Same as above.	To provide clarity we recommend revising (b) (4) (b) (4) <40 kg:..." to (b) (4) (b) (4) weighing less than 40 kg):..."
Full Prescribing Information – Section 2.1 <i>Dosage and Administration, Recommended Dosage</i>			
1.	As currently presented in Table 1, the first "Body weight group" is, (b) (4) (b) (4) (≥40Kg)" which is confusing and includes the symbols "<" and "≥".	Same as above.	To provide clarity we recommend revising (b) (4) (b) (4) (≥40Kg)" to (b) (4) (b) (4) 40 kg or greater)."
2.	As currently presented in Table 1, the second "Body weight group" is, (b) (4) (b) (4) (<40 kg)" which is confusing and includes the symbol "<".	Same as above.	To provide clarity we recommend revising (b) (4) (b) (4) (<40 kg)" to (b) (4) (b) (4) less than 40 kg)."
3.	As currently presented in both Table 1 and 2, we note that the dosing instructions include hyphens.	Prescribers may misread or become confused when determining the appropriate "Total daily dose" (Table 1) and associated "Body weight (kg)" (Table 2).	To provide consistency and clarity, consider replacing the hyphen with its intended meaning "to."
4.	As currently presented in footnote "b" of Table 1 states, "Term newborn with body weight of ≥ 2,500g". The use of the grams as the measure of	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency with other weights included throughout the PI (i.e., kg) we recommend changing the weight 2,500 g to 2.5 kg.

	weight is inconsistent with other weights included throughout the PI using kg for the measure of weight.		
5.	As currently presented in footnote "b" associated with Table 1 as well as throughout Table 2, we note the use of the symbols "<", ">", and "≥".	See "Rationale for Concern" association with line #2 under "Highlights of Prescribing Information."	To provide clarity we recommend replacing the symbols "<", ">", and "≥" with the intended meanings "less than", "greater than", and "greater than or equal to", respectively.
6.	As currently presented in both Tables 1 and 2, the units of measurement are not included after each Arabic numeral.	The missing unit of measurement may contribute to confusion that can result in medication error.	Add the appropriate units of measurement (i.e., mg/kg body weight, kg, and mg) after each Arabic numeral within Tables 1 and 2.
7.	As currently presented in Table 2, we note that the strengths include a hyphen between the Arabic numeral and mg (i.e., "30-mg" and "120-mg").	This is inconsistent with other areas of the PI in which a hyphen is not present between the Arabic numeral and mg (i.e., "30 mg" and "120 mg"). Inclusion of the hyphen can decrease readability which may contribute to confusion that can result in medication error.	To improve readability and for consistency within the PI, we recommend removal of the hyphens between the Arabic numeral and mg (i.e., "30-mg" and "120-mg") within the header of Table 2.  For example, "30 mg" and "120 mg".
Full Prescribing Information – Section 2.2 <i>Dosage and Administration</i> , (b) (4) (b) (4)			
1.	As currently presented the statement associated with the third bullet, "Apply pressure with the index finger on the (b) (4) tablet to break it	Labeling statements that are confusing may contribute to and result in medication error.	To provide clarity and improve readability, we recommend changing the statement, "Apply pressure with the index finger on the (b) (4) tablet to break it at the score line."

	at the score line" is confusing.		For example, "Apply pressure with the index finger to break the tablet at the score line."
2.	<p>As currently presented, the statement associated with the fourth bullet is</p> <p>(b) (4)</p>	<p>This important information that is associated with "Warning and Precautions" lacks prominence and may be missed and may result in a medication error due to the lack of proper medical monitoring. Additionally, according to the D&amp;A Guidance, "In unusual circumstances, certain dosing-related information may be so important for practitioners that it should precede the basic dosing information ordinarily placed at the beginning of the DOSAGE AND ADMINISTRATION section. Information should be placed above the basic dosing information only if lack of knowledge of the information or nonadherence to a recommendation would have serious consequences for patients."</p>	<p>To increase the prominence and decrease the risk of this important information being missed, relocate the statement associated with the fourth bullet, such that this statement precedes the basic dosing information.</p> <p>(b) (4)</p>
3.	<p>As currently presented the statement associated with the seventh bullet,</p> <p>(b) (4)</p> <p>"</p>	<p>Inconsistent labeling may contribute to confusion that can result in medication error.</p>	<p>To provide consistency, in the statement associated with the seventh bullet change the word (b) (4) to "prepare a slurry with."</p> <p>For example, "For patients who cannot swallow tablets, prepare a slurry by dispersing LAMPIT Tablets in water as an</p>

	(b) (4) <i>Preparation of Slurry as an Alternative Method of Administration."</i>		alternate method of administration."
Full Prescribing Information – Section 2.3 <i>Dosage and Administration, Preparation of Slurry as an Alternate Method of Administration</i>			
1.	As currently presented the statement associated with the first bullet includes (b) (4)	(b) (4) Incorrect measurement may result in wrong techniques medication errors. Thus, use of the metric system measurement (i.e., milliliter) should be used. <sup>e</sup>	Replace the (b) (4) with the metric measure "2.5 mL."  For example, "Place approximately 2.5 mL of water into a spoon."
2.	As currently presented the statement associated with the second bullet is "Place the prescribed dose into the water."	We are concerned, for example, that a dose of 2½ tablets may not disperse in 2.5 mL of water. The tablets not completely dispersing in 2.5 mL of water may result in a wrong dose medication error.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine if a dose of 2½ tablets will disperse in 2.5 mL of water.
Patient Information			
1.	As currently presented, the patient information is written to the patient audience.	Lampit is indicated "for in term newborns, infants, children and adolescents less than 18 years of age." Therefore, it would be appropriate that the	We defer to the Patient Labeling Team (PLT) to determine the appropriate audience for the "Patient Information" (i.e., patient or parent/caregiver) and if

<sup>e</sup> Institute for Safe Medication Practices. Alerts. Full Use Metric Dosing. Available from: <https://www.ismp.org/alerts/full-use-metric-dosing>. Accessed 13 APR 2020.



		"Patient Information" be written with the parent/caregiver as the audience.	needed provide the appropriate changes to the current "Patient Information" language.
2.	Under the heading "How should I take Lampit?" we note the language (b) (4) may not be patient friendly.	Incorrect measurement may result in wrong technique medication errors.	We defer to the Patient Labeling Team (PLT) to determine if (b) (4) should be changed to "2.5 mL" or if (b) (4) should be more clearly defined. Also, see recommendation above regarding use of (b) (4) measurements.

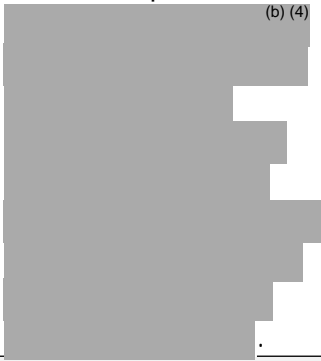
Table 3. Identified Issues and Recommendations for Bayer Healthcare Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	There is inadequate differentiation between the 30 mg and 120 mg product strength statements.	The use of (b) (4) for the product's strength statement on both the 30 mg and 120 mg products may lead to wrong strength selection errors.	<p>Revise the color scheme of the 30 mg and 120 mg strength statements (b) (4) so that the strength statements appear in their own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.</p> <p>You could consider the use of different color fonts, boxing, or some other means to provide adequate differentiation between the product strength statements (30 mg and 120 mg) on the container labels and carton labeling.</p>

Table 3. Identified Issues and Recommendations for Bayer Healthcare Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the (b) (4) statement included is (b) (4) see (D) (4) prescribing information."	This is inconsistent with the terminology (i.e., "Recommended Dosage") used in the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) see (D) (4) prescribing information." to read "Recommended Dosage: See prescribing information."
3.	The format for expiration date is not defined.	Clearly defining the expiration date format will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The intended placement for the barcode is notated on the proposed container label;	The linear barcode is often used as additional verification before drug administration in the	We request that you add the product barcode to the carton labeling.

Table 3. Identified Issues and Recommendations for Bayer Healthcare Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	however, the intended placement for barcode is not included on the carton labeling.	inpatient setting; therefore, it is an important safety feature that should be part of the labeling whenever possible.	Additionally, we recommend that the barcode on the container label be oriented to the vertical position to improve scannability, as barcodes placed in a horizontal position may not scan due to the curvature of the container.
Container Label(s)			
1.	<p>As currently presented your manufacturer name (i.e., Bayer) within your corresponding graphic design (i.e., logo), competes in prominence with the proprietary name, Lampit.</p> 	<p>The proprietary and established names should be the most prominent information on the container label.<sup>f</sup> Additionally, the product strength is considered to be “critical information.” To avoid strength confusion, the product strength statement should be prominently displayed on the principal display panel (PDP).</p>	<p>To decrease the height and prominence of your graphic design (i.e., logo), containing the manufacturer name (i.e., Bayer), we recommend relocating the graphic design (i.e., logo) away from the proprietary name (for example, to the bottom of the PDP, or to the side or back panel), as well as decreasing the height of your graphic design (i.e., logo) for “Bayer.”</p>
Carton Labeling			

<sup>f</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Table 3. Identified Issues and Recommendations for Bayer Healthcare Pharmaceuticals, Inc.  
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the strength statements (i.e., "30 mg" and "120 mg") lack prominence.	The product strength statement is considered to be "critical information." <sup>b</sup> To avoid medication errors involving strength confusion, the product strength statement should be prominently displayed on the PDP.	We recommend that you increase the prominence of the strength statement (i.e., "30 mg" and "120 mg") by relocating the strength statement such that it is closer proximity to the proprietary and established names, increasing the font size (height), bolding, and/or adding color to the strength statement.

## 5 CONCLUSION

Our evaluation of the proposed Lampit prescribing information (PI) container labels, and carton labeling, identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Bayer Healthcare Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

# APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Lampit that Bayer Healthcare Pharmaceuticals, Inc. submitted on February 27, 2020.

Table 4. Relevant Product Information for Lampit																																																													
Initial Approval Date	N/A																																																												
Active Ingredient	nifurtimox																																																												
Indication	For in term newborns, infants, children and adolescents less than 18 years of age for the treatment of Chagas disease (American Trypanosomiasis) caused by <i>Trypanosoma cruzi</i> ( <i>T. cruzi</i> ).																																																												
Route of Administration	oral																																																												
Dosage Form	tablets																																																												
Strength	30 mg (functionally scored) and 120 mg (functional scored)																																																												
Dose and Frequency	<div><ul style="list-style-type: none"><li>dosed by body weight and age of the patient</li><li>administered three times a day with food</li><li>the recommended duration of treatment is 60 days</li></ul></div> <div>Total Daily Recommended Dosages Based on Body Weight</div> <table><tr><th>Body weight group</th><th>Total daily dose of nifurtimox [mg/kg body weight]</th></tr><tr><td>(b) (4)(≥40 kg)</td><td>8–10</td></tr><tr><td>(b) (4)(<math>\geq</math>40 kg)</td><td>10–20</td></tr></table> <div>(b) (4)</div> <div><sup>b</sup>Term newborn with body weight of <math>\geq</math> 2,500g</div> <div>Individual Dosages Based on Body Weight in Pediatric Patients (0 to &lt;18 years)</div> <table><tr><th>Body weight (kg)</th><th>Dose (mg)</th><th>Number of nifurtimox 30-mg tablets per dose (3 x Daily)</th><th>Number of nifurtimox 120-mg tablets per dose (3 x Daily)</th></tr><tr><td>2.5–4.5</td><td>15</td><td>½ tablet</td><td>—</td></tr><tr><td>4.6–&lt;9</td><td>30</td><td>1 tablet</td><td>—</td></tr><tr><td>9–&lt;13</td><td>45</td><td>1 ½ tablets</td><td>—</td></tr><tr><td>13–&lt;18</td><td>60</td><td>2 tablets</td><td>½ tablet</td></tr><tr><td>18–&lt;22</td><td>75</td><td>2 ½ tablets</td><td>—</td></tr><tr><td>22–&lt;27</td><td>90</td><td>3 tablets</td><td>—</td></tr><tr><td>27–&lt;35</td><td>120</td><td>4 tablets</td><td>—</td></tr><tr><td>35–&lt;41</td><td>180</td><td>—</td><td>1 ½ tablets</td></tr><tr><td>41–&lt;51</td><td>120</td><td>—</td><td>1 tablet</td></tr><tr><td>51–&lt;71</td><td>180</td><td>—</td><td>1 ½ tablets</td></tr><tr><td>71–&lt;91</td><td>240</td><td>—</td><td>2 tablets</td></tr><tr><td>&gt;91</td><td>300</td><td>—</td><td>2 ½ tablets</td></tr></table>			Body weight group	Total daily dose of nifurtimox [mg/kg body weight]	(b) (4)(≥40 kg)	8–10	(b) (4)( $\geq$ 40 kg)	10–20	Body weight (kg)	Dose (mg)	Number of nifurtimox 30-mg tablets per dose (3 x Daily)	Number of nifurtimox 120-mg tablets per dose (3 x Daily)	2.5–4.5	15	½ tablet	—	4.6–<9	30	1 tablet	—	9–<13	45	1 ½ tablets	—	13–<18	60	2 tablets	½ tablet	18–<22	75	2 ½ tablets	—	22–<27	90	3 tablets	—	27–<35	120	4 tablets	—	35–<41	180	—	1 ½ tablets	41–<51	120	—	1 tablet	51–<71	180	—	1 ½ tablets	71–<91	240	—	2 tablets	>91	300	—	2 ½ tablets
Body weight group	Total daily dose of nifurtimox [mg/kg body weight]																																																												
(b) (4)(≥40 kg)	8–10																																																												
(b) (4)( $\geq$ 40 kg)	10–20																																																												
Body weight (kg)	Dose (mg)	Number of nifurtimox 30-mg tablets per dose (3 x Daily)	Number of nifurtimox 120-mg tablets per dose (3 x Daily)																																																										
2.5–4.5	15	½ tablet	—																																																										
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9–<13	45	1 ½ tablets	—																																																										
13–<18	60	2 tablets	½ tablet																																																										
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22–<27	90	3 tablets	—																																																										
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41–<51	120	—	1 tablet																																																										
51–<71	180	—	1 ½ tablets																																																										
71–<91	240	—	2 tablets																																																										
>91	300	—	2 ½ tablets																																																										
How Supplied	Bottles of 100 tablets																																																												

Storage	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
Container Closure	Plastic bottle 90 mL HDPE white opaque closed with screw cap PP/PP white opaque with sealing insert and child proof.

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>9</sup> along with postmarket medication error data, we reviewed the following Lampit labels and labeling submitted by Bayer Healthcare Pharmaceuticals, Inc..

- Container label(s) received on February 27, 2020
- Carton labeling received on February 27, 2020
- Prescribing Information received on February 27, 2020 available at:  
<\\cdsesub1\evsprod\nda213464\0016\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean.docx>

### F.2 Label and Labeling Images

Container label(s)

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

<sup>9</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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DEBORAH E MYERS  
04/14/2020 08:29:39 AM

OTTO L TOWNSEND  
04/14/2020 09:14:03 AM





# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 2, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Gregory DiBernardo, RPM  
DAI

Subject: QT Consult to NDA 213464 (SDN 001/004)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/11/2020 regarding the Division's QT-related question. We reviewed the following materials:

- Previous QT-IRT review for IND 109901 dated 01/07/2013 in DARRTS;
- Study 16027 [report](#) (Submission 0001);
- Proposed [label](#) (Submission 0001);
- Sponsor's response to IR requests in submissions [0009](#), [0010](#), [0013](#)
- [Investigator's brochure](#) (Submission 0004); and
- [Highlights of clinical pharmacology and cardiac safety](#) (Submission 0004).

## 1 IRT's response to the Division's questions:

**Question 1:** We request the IRT to review the QT findings from the Phase 3 trial (Study 16027)

**IRT's response:** ECG data collected in study 16027 are not adequate to support a QT assessment of nifurtimox tablets.

**Question 2:** The Applicant proposes not to include any QT related information in the product labeling. We request feedback on the acceptability of Applicant's proposal.

**IRT's response:**

- 1) Because available data are not adequate to support a QT assessment, we agree with the applicant's proposal for not including QT related information in the product label.
- 2) Nifurtimox is considered a NME drug, therefore, a thorough QT study is recommended as per ICH E14. If conducting a conventional TQT study is not possible for this product, the sponsor can characterize the QTc effects in an alternate study design to exclude large mean increases in the QTc interval as per ICH E14 Q&A 6.1. The QT assessment can be conducted in a dedicated QT study or in a sub-study in a future clinical trial. We recommend that the sponsor submit the QT assessment plan for review. When submitting the QT assessment plan, the sponsor should include the following items:
  - a. QT study protocol
  - b. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (<https://www.fda.gov/media/129685/download>)
  - c. Statistical analysis plan
  - d. Investigator's Brochure

## **2 BACKGROUND**

### **2.1 Product Information**

Nifurtimox is an antiprotozoal. The sponsor (Bayer) is seeking accelerated approval for nifurtimox tablets in term newborns, infants, children and adolescents less than 18 years of age for the treatment of Chagas disease (American Trypanosomiasis) caused by *Trypanosoma cruzi*. The proposed therapeutic dose is oral tablet with food, 3 times daily for 60 days. The exact dosing amount is determined based on body weight and age.

- (b) (4)  $\geq 40$  kg: The total daily dose is 8–10 mg/kg orally.
- (b) (4)  $< 40$  kg: the total daily dose is 10–20 mg/kg orally.

### **2.2 Sponsor's position related to the question**

Previously the IRT agreed with the sponsor's general proposal to evaluate drug effect on the QT/QTc interval using data from in vitro (i.e. voltage clamp assay in HEK293 cells transfected with the hERG K<sup>+</sup> channel) and in vivo (i.e. in conscious beagle dogs) preclinical studies as well as clinical ECG data in the Phase 3 study. The IRT recommended the sponsor to submit a detailed description of your pre-clinical plan and the clinical Phase III cardiac safety assessment plan for review (IRT review under IND 109901, dated 01/07/2013). There has been no follow-up submissions related to the QT assessment plan of this drug.

In the current submission, the sponsor provided an evaluation of drug effect on the QT/QTc interval using data from the Phase 3 study 16027. Refer to section 2.5 of this review for a summary of the findings.

### **2.3 Nonclinical Cardiac Safety**

- In vitro (GLP), exposure of HEK293 cells stably transfected with the hERG K<sup>+</sup> channel to nifurtimox was associated with concentration-dependent inhibition of the hERG-mediated

tail current amplitude. The effect of nifurtimox reached threshold (IC<sub>20</sub>) and half-maximal inhibitory concentrations (IC<sub>50</sub>) at approximately 13 µmol/L and 98 µmol/L (extrapolated), respectively.

- In vitro (non GLP), exposure of rabbit cardiac Purkinje fibers to nifurtimox in the nominal concentration range 1 to 50 µmol/L did not induce any pronounced and/or statistically significant alterations of resting membrane potential, AP amplitude, maximal upstroke velocity, and maximal repolarization velocity. Arrhythmia markers, i.e. triangulation, early after-depolarization, were negative. APD<sub>50</sub> and APD<sub>90</sub> were prolonged in a concentration-dependent manner (statistically significant at 10 µmol/L: APD<sub>50</sub> +16%, APD<sub>90</sub> +10%), however, without further increase at 50 µmol/L, and the AP plateau was shifted towards more positive potentials (+8 mV at 10 µmol/L, statistically significant). Furthermore, at stimulation rates ranging from 0.2 to 2.5 Hz, nifurtimox prolonged the APD<sub>90</sub> in a concentration-dependent, however, frequency-independent manner.
- In vivo (GLP), nifurtimox was administered orally to conscious, telemetered Beagle dogs at single doses of 0, 20, 40, and 80 mg/kg body weight. In satellite animals, mean peak plasma levels of 2670, 2290, and 5440 mg/L were obtained after oral administration of 20, 40, and 80 mg/kg of nifurtimox, respectively. When compared to control animals, nifurtimox caused a slight dose-dependent decrease in systolic blood pressure for about 11 h post-dose whereas the diastolic blood pressure remained substantially unaffected. In parallel, a slight to moderate increase in heart rate, most likely as a counter regulation to blood pressure decrease was seen. In the ECG the PQ interval and QT interval were shortened along with increased heart rate. The QTc intervals and the QRS complex were not substantially affected by oral administration of nifurtimox. No influence of nifurtimox on body temperature was seen.

In conclusion, a single oral administration of nifurtimox to conscious dogs causes a slight to moderate and transient decrease in systolic blood pressure accompanied by an increase in heart rate.

**Reviewer's Comment:** In the Phase 3 study, the maximum geometric mean  $C_{max,ss}$  value across different age groups is 464.7 ng/mL (n=11). Assuming plasma binding of 57.6% and MW of 331.3 g/mol, the ratio between hERG IC<sub>20</sub> and free  $C_{max,ss}$  is 22-fold and the ratio between IC<sub>50</sub> (extrapolated) and free  $C_{max,ss}$  is 165-fold.

## 2.4 Clinical Cardiac Safety

The sponsor did not provide a description of the total number of clinical trials or the number of subjects at different drug exposure levels. The sponsor did not provide a summary of cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).

## 2.5 Summary results of prior QTc assessments

Study 16027 is a prospective, historically controlled study to evaluate the efficacy and safety of a new pediatric formulation of nifurtimox in children aged 0 to 17 years with Chagas' disease. Approximately 300 pediatric subjects with Chagas disease were stratified into 4 age groups (Stratum 1: 0-27 days; Stratum 2: 28 days to <8 months; Stratum 3: 8 months to < 2 years;

Stratum 4: 2 years to <18 years). Within each group, patients were randomized to receive nifurtimox either as a 60-day regimen (n = 200) or a 30-day regimen (n = 100).

Changes in QT/QTc interval were evaluated in ECGs obtained at screening, at 2-4 hours post-dose at Visits 2, 3, 6 and 8, and during the follow-up period at Visits 9, 10 and 11. 12-lead ECG is optional in subjects < 5 years of age at the discretion of the investigator.

An increase in QTcB and QTcF was infrequent and was observed not only after administration of both nifurtimox and placebo, but also during the follow-up period where no study drug was administered.

In the 60-day regimen, 5 (2.6%) subjects showed absolute QTcB values >480 ms and 2 (1.0%) subjects showed absolute QTcB values > 500 ms at baseline, prior to exposure to nifurtimox; one (0.5%) subject showed an absolute QTcF value > 480 ms. No absolute QTcF values >500 ms were observed in any subject who had an ECG recording at baseline. During exposure to nifurtimox, the overall number of subjects with absolute QTcB or QTcF values > 480 ms or > 500 ms was low and tended to decrease. At the end of study treatment (Visit 8), one (0.5%) subject was observed to have a QTcB value > 480 ms; no subjects were observed to have QTcB or QTcF values > 500 ms. The same result was observed at 12-month post-treatment follow-up.

In the 30-day regimen, no subject showed absolute QTcB or QTcF values > 480 ms or > 500 ms at baseline. During exposure to nifurtimox and most of the follow-up period, one (1.1%) subject was observed to have a QTcB value > 480 ms and one (1.1%) subject was observed to have a QTcB value > 500 ms. No subject showed QTcB or QTcF values > 480 ms or > 500 ms at 12-month post-treatment follow-up.

Changes in QT/QTc interval did not result in discontinuation of study drug in any subject. No cases of QTc interval prolongation-related morbidity or mortality were observed.

The sponsor's concentration-QTc analysis does not suggest a positive exposure-response relationship between nifurtimox exposure and QTc changes from baseline.

Overall, the sponsor concluded a lack of important treatment effects on heart rate, QT/QTc intervals, PR interval, or QRS duration.

**Reviewer's comments:** Only paper ECGs were collected in study 16027, all ECG data were manually evaluated by the investigators at the local study sites, and it appears that the investigators were only blinded to the treatment (not to time). In addition, most of the paper ECGs do not come with automatic measurements from the machine. Therefore, the reviewers cannot evaluate data quality and cannot assess reader bias from the ECG data. ECG data from study 16027 is not adequate to support a QT assessment.

## 2.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cderderpqt@fda.hhs.gov](mailto:cderderpqt@fda.hhs.gov)

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