

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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

Application Type	NDA
Application Number	213464
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Reviewer Name(s)	Brad Moriyama, Pharm.D.
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Acting Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	August 5, 2020
Subject	Evaluation of Need for a REMS
Established Name	Nifurtimox
Trade Name	Lampit
Name of Applicant	Bayer Healthcare Pharmaceuticals, Inc.
Therapeutic Class	nitrofurantoin antiprotozoal agent
Formulation(s)	30 mg, 120 mg tablet
Dosing Regimen	≥ 40 kg: Total daily dose of nifurtimox 8 to 10 mg/kg. Administer nifurtimox orally three times daily for 60 days. < 40 kg: Total daily dose of nifurtimox 10 to 20 mg/kg. Administer nifurtimox orally three times daily for 60 days.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Lampit (nifurtimox) is necessary to ensure the benefits outweigh its risks. Bayer Healthcare Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 213464 for nifurtimox with the proposed indication in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas disease (American Trypanosomiasis), caused by *Trypanosoma cruzi*. The serious risks associated with nifurtimox include potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, worsening of neurological and psychiatric conditions, hypersensitivity, decreased appetite and weight loss, and porphyria. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Anti-Infectives (DAI) agree that a REMS is not necessary to ensure the benefits of nifurtimox outweigh its risks. The efficacy of nifurtimox was supported by Study 16027, in which nifurtimox was effective for the treatment of Chagas disease in pediatric patients from birth to < 18 years of age. DAI recommends accelerated approval based on the currently available data. The serious risks including potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, worsening of neurological and psychiatric conditions, hypersensitivity, decreased appetite and weight loss, and porphyria will be communicated in the warnings and precautions section of the label.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Lampit (nifurtimox) is necessary to ensure the benefits outweigh its risks. Bayer Healthcare Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 213464 for nifurtimox with the proposed indication in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas disease (American Trypanosomiasis), caused by *Trypanosoma cruzi*.¹ This application is under review in the Division of Anti-Infectives (DAI). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Lampit (nifurtimox), a NME, is a nitrofurantoin antiprotozoal agent, proposed in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas disease (American Trypanosomiasis), caused by *T. cruzi*. Nifurtimox is supplied as a 30 mg and 120 mg tablet. The proposed dosing regimen for patients ≥ 40 kg is a total daily dose of nifurtimox 8 to 10 mg/kg, and for patients < 40 kg is a total daily dose of 10 to 20 mg/kg. The total daily dose is split for administration orally three times daily for 60 days.^b Nifurtimox is currently approved in jurisdictions outside the United

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

States. Nifurtimox was first approved outside of the United States in 1970.² Nifurtimox was designated as an orphan product. If approved, the indication will be approved under the accelerated approval program based on the number of treated patients who became immunoglobulin G (IgG) antibody negative or who showed an at least 20% decrease in optical density on two different IgG antibody tests against antigens of *T. cruzi*.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for nifurtimox NDA 213464 relevant to this review:

- 08/05/2010: Orphan drug designation granted
- 12/06/2019: NDA 213464 submission in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas disease (American Trypanosomiasis), caused by *T. cruzi* received
- 03/09/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for nifurtimox

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Chagas disease is caused by a protozoan parasite *T. cruzi*.^{3,4} Worldwide, Chagas Disease affects more than 8 million people and in the United States there are estimated to be at least 300,000 cases of Chagas disease.^{5,c} Many patients that have Chagas disease in the United States are immigrants from endemic countries where Chagas disease is present.^{4,6} Chagas Disease is transmitted by insect vectors called triatomines, also known as “kissing bugs” that carry the *T. cruzi* parasite.⁷ Transmission may also occur congenitally, by blood and blood products, by solid organ transplant from infected donors, or through contaminated food or beverages.⁶ Acute infection may be asymptomatic, but could also include mild to moderate itching or rash at the site of the insect bite, or loss of appetite.⁸ Clinical symptoms may include mild to moderate hepatomegaly and/or enlargement of the lymph nodes. Chronically infected patients may also be asymptomatic.^{5,6} However, gastrointestinal or cardiac complications may occur in 20% to 30% of patients with chronic infection, which may impair a patient’s quality of life or be fatal.^d

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

The CDC guidelines for antiparasitic treatment of Chagas Disease recommend treatment for all cases of acute or reactivated Chagas disease and for chronic *T. cruzi* infection in children up to age 18.⁹ In addition, treatment in adults up to 50 years old with chronic infection who do not already have advanced cardiomyopathy is strongly recommended. The CDC guidelines list benznidazole and nifurtimox for the treatment of *T. cruzi* infection. Benznidazole, a nitroimidazole antimicrobial, was approved by the FDA in 2017 in pediatric patients 2 to 12 years of age for the treatment of Chagas disease (American trypanosomiasis) caused by *T. cruzi*.¹⁰ Benznidazole was approved under accelerated approval based on the number of treated patients who became IgG antibody negative against the recombinant antigens of *T. cruzi*. The serious risks associated with benznidazole include potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, hypersensitivity skin reactions, central and peripheral nervous system effects, and hematological manifestations of bone marrow depression. Nifurtimox is currently available from the CDC under investigational protocols.

4 Benefit Assessment

The pivotal trial NCT 026225974 (Study 16027) supporting this application for efficacy and safety consisted of a Phase 3, double-blind, randomized, prospective study which evaluated nifurtimox for the treatment of Chagas disease.^{1,11} Patients in this study were enrolled in Argentina, Bolivia, and Colombia and were patients birth to < 18 years of age and weighing at least 2.5 kg. Patients (N=330) were randomized to nifurtimox for 60 days (N=219) or nifurtimox for 30 days (N=111). The nifurtimox dosing regimen for patients \geq 40 kg was a total daily dose of nifurtimox 8 to 10 mg/kg and for patients < 40 kg was a total daily dose of nifurtimox 10 to 20 mg/kg. Nifurtimox was administered orally three times daily. The primary efficacy endpoint was cure or positive response as the combination of seroreduction defined as a \geq 20% reduction in optical density by lysate ELISA and recombinant ELISA at 12 months compared to baseline in subjects \geq 8 months to <18 years of age or seroconversion defined as negative immunoglobulin G concentration at 12 months in all patients. The primary efficacy endpoint for the lysate ELISA was 32% in the nifurtimox 60 day group and 19% in the nifurtimox 30 day group (difference 13%, 95% confidence interval 3.5 to 22.6, p=0.007). The primary efficacy endpoint for the recombinant ELISA was 35% in the nifurtimox 60 day group and 22% in the nifurtimox 30 day group (difference 13%, 95% confidence interval 3.2 to 23, p=0.010). The FDA clinical reviewer concluded that nifurtimox was effective for the treatment of Chagas disease in pediatric patients from birth to < 18 years of age.^e

5 Risk Assessment & Safe-Use Conditions

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

The safety of nifurtimox was evaluated in a Phase 3 clinical trial for the treatment of Chagas disease (NCT 026225974, Study 16027).^{1,11,f} In the safety population, 330 patients received nifurtimox (219 patients in the 60 day treatment group and 111 patients in the 30 day treatment group).

Discontinuation due to an adverse event occurred in 14/330 (4.2%) of patients, with 12/219 (5.5%) in the nifurtimox 60 day treatment group and 2/111 (1.8%) in the nifurtimox 30 day treatment group. Common adverse reactions reported with nifurtimox in the 60 day treatment group included vomiting, abdominal pain, headache, decrease appetite, nausea, rash, and pyrexia.

The serious risk⁹ associated with nifurtimox which include potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, worsening of neurological and psychiatric conditions, hypersensitivity, decreased appetite and weight loss, and porphyria are summarized in the sections below.

5.1 POTENTIAL FOR GENOTOXICITY AND CARCINOGENICITY

Nifurtimox has been reported to cause genotoxicity in humans, in several bacterial species and mammalian cell systems *in vitro*, and in rodents *in vivo*. In addition, nitrofurans agents have been reported to cause carcinogenicity with chronic treatment in mice and rats. It is unknown if nifurtimox is associated with carcinogenicity in humans. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 EMBRYO-FETAL TOXICITY

Nifurtimox may cause fetal harm based on animal studies. A Division of Pediatric and Maternal Health (DPMH) consult indicated that limited clinical data is available with nifurtimox in pregnancy in humans.¹² As nifurtimox has the potential for use in females of reproductive potential, DPMH recommended a PMR for a single-arm pregnancy safety study. The proposed label advises patients of the potential risk of embryo-fetal harm. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting nifurtimox and that effective contraception be used during treatment and for 6 months after the last dose. In addition, in males with a female partner of reproductive potential it is recommended that condoms be used during treatment and for 3 months after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 WORSENING OF NEUROLOGICAL AND PSYCHIATRIC CONDITIONS

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

⁹ Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Worsening of a patient's neurological and psychiatric condition may occur in patients with a history of brain injury, seizures, psychiatric disease, or serious behavioral alterations treated with nifurtimox. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4 HYPERSENSITIVITY

Section 5.4 of the draft labeling indicates that hypersensitivity has been reported with nifurtimox. Hypersensitivity reactions may include hypotension, angioedema, dyspnea, pruritis, rash or other severe skin reactions. Nifurtimox is contraindicated in patients with known hypersensitivity to nifurtimox or to any excipients in nifurtimox. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.5 DECREASED APPETITE AND WEIGHT LOSS

Decreased appetite and weight loss have been reported with nifurtimox. The proposed label recommends checking body weight every 14 days and to adjust nifurtimox dosage accordingly if body weight decreases during treatment. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.6 PORPHYRIA

Acute attacks of porphyria may be precipitated by treatment with nitrofurantoin derivatives. If approved, this risk will be communicated in the warnings and precautions section of the label.

During the review of nifurtimox NDA 213464 proposed label, this reviewer asked if added precautions would be needed when splitting tablets as recommended in the proposed label as the warnings and precautions section lists the risks of potential for genotoxicity and carcinogenicity and embryo-fetal toxicity. The DAI team stated that the risk of exposure for those persons splitting the tablets was low with nifurtimox. The benznidazole label also contains recommendations on tablet splitting, the warnings and precautions section list the risks of potential for genotoxicity and carcinogenicity and embryo-fetal toxicity, and no additional precautions such as gloves are recommended in the label.

6 Expected Postmarket Use

If approved, nifurtimox will primarily be used in both inpatient and outpatient settings. The likely prescribers will be infectious diseases specialists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for nifurtimox beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of nifurtimox on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on

the number of treated patients who became IgG antibody negative or who showed an at least 20% decrease in optical density on two different IgG antibody tests against antigens of *T. cruzi*. The efficacy of nifurtimox was demonstrated in Study 16027, in which nifurtimox was effective for the treatment of Chagas disease in pediatric patients from birth to < 18 years of age. The serious risks associated with nifurtimox of potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, worsening of neurological and psychiatric conditions, hypersensitivity, decreased appetite and weight loss, and porphyria will be communicated in the warnings and precautions section of the label.

Worldwide Chagas Disease affects more than 8 million people and in the United States there are estimated to be at least 300,000 cases of Chagas disease. Acute infection may be asymptomatic, but may also include mild to moderate itching, rash at the site of the insect bite, loss of appetite, mild to moderate hepatomegaly, and/or enlargement of the lymph nodes. Chronically infected patients may also be asymptomatic. However, gastrointestinal or cardiac complications may occur in 20% to 30% of patients with chronic infection, which may impair a patient's quality of life or be fatal. The likely prescribers will be infectious diseases specialists who should be knowledgeable about managing the serious adverse events reported with nifurtimox. If approved, based on the efficacy and risks associated with nifurtimox in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas disease (American Trypanosomiasis), caused by *T. cruzi*, the DRM and DAI agree that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for nifurtimox to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

- ¹ Proposed prescribing information for nifurtimox as currently edited by FDA, July 27, 2020.
- ² Bayer Healthcare Pharmaceuticals, Inc. Nifurtimox. Module 2.5. Clinical Overview. December 6, 2019.
- ³ Redd, N. Division of Risk Management NME review for benznidazole, May 24, 2017.
- ⁴ Manne-Goehler J. Chagas Disease in the United States: Out of the Shadows. Clin Infect Dis. 2017;64(9):1189-1190.
- ⁵ Bennett C, Straily A, Haselow D, et al. Chagas Disease Surveillance Activities - Seven States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(26):738-741.
- ⁶ Pérez-Molina JA, Molina I. Chagas disease. Lancet. 2018;391(10115):82-94.

⁷ Montgomery SP, Parise ME, Dotson EM, Bialek SR. What Do We Know About Chagas Disease in the United States?. *Am J Trop Med Hyg.* 2016;95(6):1225-1227.

⁸ Sueth-Santiago V, Decote-Ricardo D, Morrot A, Freire-de-Lima CG, Lima ME. Challenges in the chemotherapy of Chagas disease: Looking for possibilities related to the differences and similarities between the parasite and host. *World J Biol Chem.* 2017;8(1):57-80.

⁹ Centers for Disease Control and Prevention. Antiparasitic Treatment. Parasites – American Trypanosomiasis (also known as Chagas Disease). Accessed July 18, 2020. (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)

¹⁰ Benznidazole package insert. Florham Park, NJ: Exeltis USA, Inc.; 2017 August.

¹¹ Nifurtimox NDA 213464 multi-disciplinary review and evaluation. Accessed July 16, 2020.

¹² Division of Pediatric and Maternal Health consult to NDA 213464. July 1, 2020.

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