CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214429Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	214429
PDUFA Goal Date	November 12, 2020
OSE RCM #	2020-482; 2020-484
Reviewer Name(s)	Leah Hart, PharmD
Team Leader	Naomi Boston, PharmD
Acting Deputy Division Director	Doris Auth, PharmD
Review Completion Date	November 12, 2020
Subject	Evaluation of Need for a REMS
Established Name	Fexinidazole
Trade Name	Fexinidazole (b) (4)
Name of Applicant	Sanofi-Aventis US LLC
Therapeutic Class	Nitroimidazole antiprotozoal
Formulation(s)	Tablet for oral use
Dosing Regimen	(b) (4)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Fexinidazole (b) (4) (fexinidazole) is necessary to ensure the benefits outweigh its risks. Sanofi-Aventis US LLC submitted a New Drug Application (NDA) 214429 for fexinidazole with the proposed indication of treatment of both the first stage (hemolymphatic or stage 1) and second stage (meningo-encephalitic or stage 2) of human African Trypanosomiasis (HAT) due to *Trypanosomia brucei (T.b.) gambiense* (g-HAT) in adults and pediatric patients (6 years and older and weighing at least 20 kg (b) (4) The serious risks associated with the use of fexinidazole are QT prolongation, Central Nervous System (CNS) and psychiatric-related adverse reactions, risk of infection, hepatotoxity, and disulfiram-like reactions. The applicant did not submit a proposed REMS or risk management plan with this application but proposed Prescribing information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information.

The Division of Risk Management (DRM) and Division of Anti-infectives (DAI) have determined that if approved, a REMS is not necessary to ensure the benefits of fexinidazole outweigh its risks. Fexinidazole will have controlled access and distribution programs. In the US, fexinidazole will be stocked and prepositioned at the CDC (Atlanta, GA) by the WHO to ensure available for any potential g-HAT patient presenting locally. Prescribers will be required to contact the CDC and be instructed on how to access fexinidazole. The risks identified in the draft label are risks that these providers have likely encountered in their practice experience and can be managed without additional risk mitigation measures. In addition, the WHO interim guidelines for the treatment of g-HAT addresses the use of fexinidazole and the risks associated with its use[6].

Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of fexinidazole for treatment of both the first stage (hemolymphatic or stage 1) and second stage (meningo-encephalitic or stage 2) of human African Trypanosomiasis (HAT) due to *Trypanosomia brucei (T.b.) gambiense* (g-HAT) in adults and pediatric patients (6 years and older and weighing at least 20 kg).

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Fexinidazole (b) (4) (fexinidazole) is necessary to ensure the benefits outweigh its risks. Sanofi-Aventis US LLC submitted an NDA 214429 for fexinidazole with the proposed indication of treatment of g-HAT. 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

Fexinidazole, a new molecular entity[a], is a nitroimidazole anti-infective agent proposed for the treatment of both first stage (hemolymphatic or state 1) and second stage (meningo-encephalitic or stage 2) g-HAT. Fexinidazole is a 2-substituted 5-nitroimidazole compound that is rapidly metabolized in vitro via hepatocytes to the fexinidazole sulfoxide and fexinidazole sulfone which provide most if not all the trypanocidal activity against *Trypanosomia brucei gambiense* strains of the parasite. Fexinidazole is proposed as 600 mg tablets for oral administration once daily for 10 days with food. The recommended dose is described in Table 1 below.

Table 1: Recommended Dosage of Fexinidazole in Adults and Pediatric Patients (b) (4)

Body weight	Recommended dosage	Duration of treatment
Greater than or equal to 35 kg	Loading dose: 1800 mg (3 tablets) Maintenance dose: 1200 mg (2 tablets)	4 days 6 days
Greater than or equal to 20 and less than 35 kg	Loading dose: 1200 mg (2 tablets) Maintenance dose: 600 mg (1 tablet)	4 days 6 days

Fexinidazole is approved in the Democratic Republic of Congo (2019) and recommended in November 2018 by the European Medicines Agency under Article 58[b].

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for [Application/Number] relevant to this review:

- 03/12/2020: NDA 214429 submission for the treatment of both the first stage (hemolymphatic or stage 1) and second stage (meningo-encephalitic or stage 2) of human African Trypanosomiasis (HAT) due to *Trypanosomia brucei (T.b.) gambiense* (g-HAT) in adults and pediatric patients (6 years and older and weighing at least 20 kg (b) (4)
- 06/26/2020: 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 fexinidazole

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

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

[b] Article 58 of Regulation (EC) No 726/2004 allows the European Medicines Agency's Committee for Medicinal Products for Human Use to give opinions, in co-operation with the World Health Organization, on medicinal products for human use that are intended exclusively for markets outside of the European Union.

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a vector borne parasitic disease caused by an extracellular protozoa belonging to the genus, *Trypanosoma*, species, *brucei.* HAT is primarily transmitted through the bite of the tsetse fly. Two subspecies of *Trypanosoma brucei* are pathogenic for humans: *T. b. gambiense* and *T. b. rhodesiense*. These two parasites cause distinct pathologic entities, both of which are included under the general term HAT, but they have to be considered as two separate diseases, with different epidemiological and clinical patterns and different patient management.[1] This tropical disease occurs in sub-Saharan Africa, with the Democratic Republic of the Congo being the country with the heaviest burden of g-HAT.

Generally, both forms of the disease lead to death if untreated[c]. While *T. b. rhodesiense* (r-HAT) disease is typically acute, progressing to second-stage disease within a few weeks, and death within 6 months, g-HAT follows a progressive course, with a mean duration estimated at 3 years.[2,3,4] The stage of the disease is diagnosed by the number of white blood cells found in the cerebrospinal fluid (CSF) through a lumbar puncture. The first stage is defined as $\leq$ 5 WBC/μl and no trypanosomes in the CSF; the second stage >5 WBC/μL and/or trypanosomes in the CSF. A lumbar puncture is only required for patients with clinical symptoms and signs suggestive of severe meningo-encephalitic stage (stage 2).

In 2012 the WHO targeted HAT for elimination as a public health problem, set to be achieved by 2020. HAT is found exclusively in Africa, with the majority of cases occurring in the Democratic Republic of Congo. There are no cases in the United States[5]. In 2018, 977 cases were reported globally, down from 2164 in 2016. This is close to the 2020 target of a 90% reduction from the 2000-2004 baseline. Even though r HAT health facilities have decreased in number and coverage, *T. b. gambiense* healthcare facilities have continued to increase, with a better coverage of at-risk populations. For *gambiense* HAT, approximately 31, 42, and 47 million people at risk are respectively within one-, three- and five-hour travel of a facility offering diagnosis.[d] The WHO is now aiming for a 2030 goal of "zero cases", including the interruption of the transmission of g-HAT.[6]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Antitrypanosomal treatment is indicated for all persons diagnosed with HAT and the choice of therapy depends on the infecting species and the disease stage. Focusing on treatment for T.b. gambinese, the treatment depends on the stage of the disease[7]. Treatment for g-HAT consists of four medications: eflornithine with or without nifurtimox, melarsoprol, pentamidine and suramin, although only pentamidine and nifurtimox are FDA approved. The remaining treatments are only able to be acquired from the Centers for Disease Control (CDC). First line treatment for g-hat is pentamidine for first stage and a nifurtimox-eflornithine combination therapy (NECT) for second stage disease. Eflornithine and melarsoprol monotherapies are second- or third-line alternatives and rarely used.[6]See the chart below. Pentamidine is FDA approved

[c] 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.*

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

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Nifurtimox (Lampit)[8]	Treatment of Chagas disease (American Trypanosomiasis), caused by *Trypanosoma cruzi*	Total daily recommended dosages of nifurtimox are based on the body weight of the patient and administered three times daily	Potential for genotoxicity and carcinogenicity; embryo fetal toxicity; worsening of neurological and psychiatric conditions; hypersensitivity; decreased appetite and weight loss; and porphyria	No boxed warning, a medication guide is included in labeling
Pentamidine[9]	Nebulizer formulation for the prevention of *Pneumocystis jiroveci* pneumonia (PJP) in high-risk, HIV-infected patients Injectable formulation for the treatment of pneumonia due to *Pneumocystis carinii*	300mg either deep IM injection or IV administration over a period of 60-120 minutes	Severe hypotension (may result after a single IM or IV dose and is more likely with rapid IV administration so patients are recommended to be lying down and blood pressure monitored closely during administration with equipment for emergency resuscitation should be readily available; hypoglycemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, both by the IM and IV routes.	No boxed warning, no medication guide
Other Treatments Eflornithine- most common (>10%) reported adverse events include fever, pruritus, hypertension, cough, anorexia, nausea or vomiting, diarrhea, abdominal pain and headaches. Seizures occur in 4-10% of cases but are generally				

isolated or respond to treatment.[10]
Melarosoprol- the adverse events may be severe and life threatening including encephalopathic syndrome which occurs in 5-18% of all treated cases and which is fatal in 10-70% of these patients.[11,12]
Suramin- The most frequent adverse reactions are nausea, vomiting, diarrhea, abdominal pain, and a feeling of general discomfort. The most serious adverse events are rare, with the exception of pyrexia and nephrotoxicity. Nephrotoxicity is usually mild and reversible.[13,14]

Fexinidazole, approved in the Democratic Republic of Congo, is now the first-choice treatment in patients aged ≥6 years and body weight ≥ 20 kg presenting without clinical features consistent with state 2 or presenting with <100 WBC/μL according to the newest WHO Guidelines.[6]

4 Benefit Assessment

Fexinidazole efficacy and safety were evaluated in a randomized, comparative open-label study conducted in late stage 2 HAT adult patients (DNDiFEX004) and additional plug-in studies in stage 1 or early stage 2 of g-HAT in adult patients (DNDiFEX005) and children aged ≥6 years and weighing ≥20 kg with all stages of HAT (DNDiFEX006)[15].

DNDiFEX004

This was a randomized, open-label, multicenter, non-inferiority study in adult patients with late stage 2 HAT due to *T. b. gambiense*. Patients (n=394) were randomized in a 2:1 ratio to a 10-day treatment regimen of either fexinidazole (n=264) or NECT (n=130). The mean age was 35 (range 15 to 71) and 61% were male. The fexinidazole group received 1800 mg of fexinidazole orally once daily for Days 1 through 4, followed by 1200 mg orally once daily for Days 5 through 10, with all dosing in the fed state.

The primary efficacy objective was to demonstrate a noninferior success rate of fexinidazole to NECT at 18 months after the EOT, with the margin of acceptable difference at 13%. Month 18 success rates were 91.2% for fexinidazole versus 97.6% for NECT (difference fexinidazole-NECT -6.42%, 97.06% CI [-11.22; -1.61]) and 1358). The three studies were similar in design: multicenter, randomized, double-blind, and placebo-controlled. Each of these studies had the same primary efficacy endpoint: the reduction in POS frequency over the placebo group. A 20% reduction over placebo reflects a clinically relevant reduction, and all three studies were powered to detect a 20% reduction over placebo.

DNDiFEX005

This was an open-label, single-arm, multicenter study in adult patients with stage 1 (n=189) and early stage 2 (n=41) HAT due to *T. b. gambiense*, fexinidazole was given as in DNDiFEX004. The mean age was 34 (range 15 to 73) and 50% were male. The primary efficacy objective was to demonstrate a fexinidazole success rate greater than 80% at 12 months after the end of treatment (EOT). At Month 12 the overall success rate was 98.7%, 95% CI (96.2; 99.7).

DNDiFEX006

This was an open-label, single-arm, multicenter study in patients aged 6 to ≤15 weighing at least 20 kg with stage 1 (n=69), early (n=19), or late (n=37) stage 2 HAT due to *T. b. gambiense*. fexinidazole 1200 mg was given in fed condition once a day on Days 1 through 4, followed by 600 mg on Days 5 through 10 to patients weighing <35 kg and all other patients received the adult dosing regimen. The primary efficacy objective was to demonstrate a fexinidazole success rate greater than 80% at 12 months after the EOT. The overall success rate at 12 months was 97.6%, 95% CI (93.1; 99.5).

All Fexinidazole Pooled Data (studies DNDiFEX004 DNDiFEX005 DNDiFEX006)

The success rates in g-HAT patients (adults and children, all stages, one dose of fexinidazole at least) ranged between 97% and 100% for up to 100 WBC/µL in the CSF at baseline, but it decreased to 88.6% when the CSF WBC count was above 100.

The Medical Officer (MO) has concluded that *the Applicant has provided substantial evidence of effectiveness to support approval of fexinidazole for the treatment of first and second stage g-HAT in patients aged 6 or older who weigh 20 Kg or more. A single adequate and well-controlled noninferiority trial demonstrated that fexinidazole was noninferior to nifurtimox-eflornithine combination therapy (NECT) for the treatment of late second-stage g-HAT. Two supplemental single-arm trials provided additional clinical data: a trial in adults with stage 1 and early stage 2 disease and a trial in pediatric patients with both disease stages. Additional supporting information was provided by in vitro microbiology studies, and animal models of infection demonstrating the activity of fexinidazole*.[e,16]

5 Risk Assessment & Safe-Use Conditions

The safety of fexinidazole in the treatment of gHAT has been evaluated in three clinical trials; one Study DNDiFEX004 compared the safety of fexinidazole to NECT treatment in late stage 2 HAT patients (N=394); two plug-in studies: Study DNDiFEX005 assessed the safety of fexinidazole in stage 1 and early stage 2 HAT patients (N=230); and Study DNDiFEX006 assessed the safety of fexinidazole in children aged 6 years or older with any stage HAT (N=125).

The pooled HAT studies included a total of 749 patients who received at least one dose of study medication, including 130 patients in the NECT treatment arm and 619 patients in the fexinidazole treatment arm. Patients were followed for up to 18 months from the time of treatment completion.

The most frequently reported adverse reactions (≥5%) in the pooled fexinidazole group (619 patients) were as follows: vomiting (38%), nausea (33%), asthenia (20%), decreased appetite (17%), headache

[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.*

(16%), insomnia (15%), tremor (14%), dizziness (14%), dyspepsia (12%), feeling hot (8%), salivary hypersecretion (8%), and abdominal pain upper (8%).[f]

Fexinidazole is structurally similar to nitroimidazole class drugs. Nitroimidazole class adverse reactions may include: QT prolongation, gastrointestinal disorders, psychiatric disorders, and liver function test disorders.

5.1 QT INTERVAL PROLONGATION

QT prolongation is a nitroimidazole class adverse reaction. Fexinidazole tablets have been shown to prolong the QT interval in a concentration-dependent manner; causing on average an increase of 19 msec (milliseconds) in the QTcF interval. In clinical trials, three (<1%) patients in the fexinidazole group had a QTcF value of >500 msec versus none in the NECT group. The proposed label warns to avoid fexinidazole in patients who have:

a. QTcF interval greater that 470 msec and/or:

b. History of Torsades de pointes, congenital long QT syndrome, cardiac arrhythmias, uncompensated heart failure, or family history of sudden death

c. Uncorrected hypokalemia

The label also warns to avoid concomitant administration of fexinidazole tablets with other drugs that are known to prolong the QT interval, those that block cardiac potassium channels, and/or those that induce bradycardia. In addition, to avoid concomitant administration of fexinidazole tablets with drugs that are inducers of hepatic cytochrome P450 due to the potential increase of fexinidazole's active metabolites. The concentration of one of the active metabolites of fexinidazole, fexinidazole sulfone, has been associated with increased QT prolongation risks.

The label also recommends that (b) (4)

5.2 PSYCHIATRIC EVENTS

Psychiatric events are considered a nitroimidazole class effect. Adult patients treated with fexinidazole reported a higher percentage of psychiatric related events (> 1%), including insomnia, agitation, anxiety, psychotic disorder, abnormal behavior, depression, logorrhea, nightmare and personality change than those treated with NECT in the clinical study. These events also occurred in pediatric patients. Most were mild to moderate severity and did not result in treatment discontinuation. Suicidal ideation has also been observed with fexinidazole tablets. Psychiatric adverse events will be included in Warnings and Precautions, instructing patients with psychiatric disorders (history or acute) be hospitalized during

[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.*

the entire treatment. The WHO interim guidelines for g-HAT also state that hospitalizations should be mandatory for patients with psychiatric disorders.

5.3 Risk of Infection secondary to drug-induced neutropenia

Neutropenia is a nitroimidazole class effect. Although no cases of infectious complications were reported in the clinical studies, cases of severe neutropenia were reported in patients treated for Chagas disease (not an approved indication) with higher total doses of fexinidazole. In the HAT studies, fexinidazole caused mild decrease in ANC (~500 per µL). Therefore, fexinidazole should be used with caution in patients with evidence, or history, of blood dyscrasia and instructed to return to the clinic if they develop fever within 3 months of the end of treatment.

5.4 Potential for Hepatotoxicity

A reversible increase in transaminase was observed in some patients treated with fexinidazole in the clinical studies. In the Phase I Study DNDiFEX001, there was 1 case of transient ALT increase up to 30 x ULN in a patient who received a high dose of 3600 mg/day for 14 days, with mild clinical symptoms and rapid resolution. These observations were reversible, although in 22.5% the signs persisted over 3 months. In a Chagas disease study 40% of patients experienced chronic or acute increase in ALT and 22.5% in AST >3 x ULN (versus none in the placebo arm), although PK/PD analysis supports difference between HAT and Chagas. Fexinidazole showed no clinically evident drug-induced hepatic injury in HAT patients. Hepatotoxicity is considered a Nitroimidazole class effect (b) (4) . In the HAT clinical studies there were no cases of severe hepatoxicity, no Hy's law cases were reported, and no clinically significant increase in transaminase was reported in HAT patients treated with fexinidazole.

6 Expected Postmarket Use

Fexinidazole will have controlled access and distribution programs. In the US, fexinidazole will be stocked and prepositioned at the CDC (Atlanta, GA) by the WHO to ensure available for any potential g-HAT patient presenting locally. Prescribers will be required to contact the CDC and be instructed on how to access the product.

In addition, the label recommends that (b) (4)

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

Fexinidazole is a nitroimidazole anti-infective agent proposed for the treatment of both first stage (hemolymphatic or state 1) and second stage (meningo-encephalitic or stage 2) human African trypanosomiasis (HAT) due to *Trypanosoma brucei (T. b.) gambiense* (g-HAT). When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risk for fexinidazole, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. Fexinidazole will have controlled access and distribution programs. In the US, fexinidazole will be stocked and prepositioned at the CDC (Atlanta, GA) by the WHO to ensure available for any potential g-HAT patient presenting locally. Prescribers will be required to contact the CDC and be instructed on how to access the product. The risks identified in the draft label are risks that these providers have likely encountered in their practice experience and can be managed without additional risk mitigation measures. In addition, WHO interim guidelines for the treatment of g-HAT addresses the use of fexinidazole and the risks associated with its use.

At the time of this review, labeling negotiations were still ongoing with the Applicant. DRM and DAI have determined that if approved, a REMS is not necessary to ensure the benefits of fexinidazole outweigh its risks. The most concerning adverse reactions observed with the use of fexinidazole are QT prolongation, psychiatric-related adverse reactions, risk of infection and hepatotoxicity. The AEs reported in the clinical trials for fexinidazole were similar to currently approved nitroimidazole drugs, but not similar to other currently approved drugs used to treat g-HAT.

If fexinidazole is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with fexinidazole. At this time, none of these risks will receive a boxed warning in the label.

The Clinical Reviewer recommends approval of fexinidazole on the basis of the efficacy and safety information currently available.

9 Conclusion & Recommendations

If approved, DRM and DAI have determined that a REMS is not necessary to ensure the benefits outweigh the risks of fexinidazole. The management of the risks associated with fexinidazole treatment will be communicated through labeling. Should DAI have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

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[9] Pentamadine Prescribing Information (last updated May 1, 2019)

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[15] Draft Prescribing Information for fexinidazole as currently edited by the FDA, last updated October 22, 2020.

[16] Shrimant, M. Division of Anti-infectives. Clinical Review for fexinidazole NDA 214429, November 12, 2020.

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/s/

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