EU-RISK MANAGEMENT PLAN FOR FEXINIDAZOLE WINTHROP® (FEXINIDAZOLE)

Data Lock Point (DLP)	06-SEP-2022
RMP Version number	Version 3.1
Date of final sign-off	26-SEP-2023

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk management plan v3.1 is prepared to address Type II variation assessment report comments, dated 14-Sep-2023, on RMP v3.0 (submitted within procedure No. EMEA/H/W/002320/II/0016) and to update PASS (FEXINC09395) milestones as per revised protocol v2.0 submitted within procedure EMEA/H/W/002320/MEA/002.2. Risk management plan version 3.0 is updated in context of extension of indication application of HAT due to *Trypanosoma brucei rhodesiense* and to include newly important potential risk of Hepatotoxicity in Cockayne Syndrome patients.
Summary of significant changes in this RMP	Risk management plan version 3.0 updated to include data from recently completed clinical study FEX-007 for newly proposed indication of HAT due to *T. b. rhodesiense*. Risk management plan Part II Module SI, SIII and SIV updated for recently completed clinical study FEX-007 and newly proposed indication of HAT due to *T. b. rhodesiense*. Risk management plan version 3.0 Part II Module SVII, SVIII, Part V and Part VI updated to include important potential risk of Hepatotoxicity in Cockayne Syndrome patients. **Safety concerns:** • List of safety concerns revised in context of recently emerged safety concern. • Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)" has been included as important potential risk. • Important potential risk "Development of resistance to fexinidazole, cross resistance between fexinidazole and nifurtimox" has been updated to indication specific risk "Development of resistance to fexinidazole (For *Trypanosoma brucei gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)". As per Type II variation assessment report comments on EU-RMP v3.0, the following safety concern is updated in EU-RMP v3.1: • Important potential risk of "Vomiting" has been reclassified to important identified risk in the list of safety concerns. **Pharmacovigilance Plan:** Post-authorization safety study (FEXINC09395) milestones are updated in line with revised PASS protocol (version 2.0) submitted within procedure EMEA/H/W/002320/MEA/002.2. **Risk minimization measures:** Update of Part V and Part VI in line with the revised list of safety concerns and new DLP. **Annexes:** Annex 2 updated to include revised milestone of PASS (FEXINC09395). Annex 3 updated to include revised PASS (FEXINC09395) study protocol version 2.0.

CS: Cockayne Syndrome; CYP: Cytochrome P450; DLP: Data Lock Point; EU: European Union; HAT: Human African Trypanosomiasis; PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not Applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	2.1
Approved with procedure	EMEA/H/W/002320/PSUV/0008
Date of approval (opinion date)	16-Dec-2021

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ADR:	Adverse Drug Reaction
AE:	Adverse Event
ALP:	Alkaline Phosphatase
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under Curve
BPM:	Beats Per Minute
BTT:	Bitherapy Trial
CAR:	Central African Republic
CI:	Confidence Interval
CNS:	Central Nervous System
COVID-19:	Coronavirus Disease
CS:	Cockayne Syndrome
CTCAE:	Common Terminology For Adverse Event
CYP:	Cytochrome P450
DALA:	Drug Abuse Liability Assessment
DDI:	Drug-Drug Interaction
DEC:	Disease Endemic Countries
DLP:	Data Lock Point
DRC:	Democratic Republic of Congo
ECG:	Electrocardiogram
eCTD:	Electronic-Common Technical Document
EEA:	European Economic Area
EMA:	European Medicines Agency
EoH:	End of hospitalization
EoT:	End of Treatment
EPAR:	European Public Assessment Report
EU:	European Union
FDA:	Food Drug and Administration
FSI:	First Subject In
g-HAT:	*Gambiense* Human African Trypanosomiasis
GLP:	Good Laboratory Practice
HAT:	Human African Trypanosomiasis
HCP:	Healthcare Professional
hERG:	Ether-a-go-go-Related Gene
HR:	Heart Rate
IHME:	Institute for Health Metrics and Evaluation
IM:	Intramuscular
INN:	International Nonproprietary Name
ITT:	Intent-To-Treat
IV:	Intravenous

LFT:	Liver Function Test
MA:	Marketing Authorization
MedDRA:	Medical Dictionary for Regulatory Activities
MoA:	Mechanism of Action
MSF:	Médecins Sans Frontières/Doctors Without Borders
NADH:	Nicotinamide Adenine Dinucleotide
NCI:	National Cancer Institute
NCS:	Non-Clinical Significant
ND:	No Data
NDA:	New Drug Application
NECT:	Nifurtimox-Eflornithine Combination Therapy
NSSCP:	National Sleeping Sickness Control Program
PASS:	Post-Authorization Safety Study
PBRER:	Periodic Benefit Risk Evaluation Report
PD:	Pharmacodynamic
PHP:	Public Health Program
PIP:	Pediatric Investigation Plan
PK:	Pharmacokinetic
PL:	Package Leaflet
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
PV:	Pharmacovigilance
Q:	Quarter
QPPV:	Qualified Person Responsible for Pharmacovigilance
QTcF:	Corrected QT Interval by Fridericia
r-HAT:	*Rhodesiense* Human African Trypanosomiasis
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SmPC:	Summary of Product Characteristics
SOC:	System Organ Class
TdP:	Torsades de pointes
TEAE:	Treatment Emergent Adverse Event
ULN:	Upper Limit of Normal
US:	United States
USPI:	United States Prescribing Information
UV-A:	Ultraviolet-A
VL:	Visceral Leishmaniosis
WBC:	White Blood Cell
WHO:	World Health Organization

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Fexinidazole
Pharmacotherapeutic group(s) (ATC Code)	P01CA03
Marketing Authorization Holder or Applicant	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	FEXINIDAZOLE WINTHROP
Marketing authorization procedure	Article 58 application.
Brief description of the product	Chemical class: Fexinidazole is a 2-substituted 5-nitroimidazole compound belonging to a wider class of nitroimidazole anti-infective agents.
	Summary of mode action: Fexinidazole is rapidly metabolized in vitro via animal and human hepatocytes to the fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2). The compound acts as a biologically active pro drug with the sulfoxide and sulfone metabolites providing most if not all of the trypanocidal activity in vitro and in vivo against *T.b. gambiense* strains of the parasite. The most active metabolite is considered to be fexinidazole sulfone (M2).
	Important information about its composition: The product contains lactose monohydrate as an excipient from animal origin.
Hyperlink to the product information	Refer to eCTD sequence 0029, Module 1.3.1 Proposed Product Information.
Indication(s) in the EEA	Current: FEXINIDAZOLE WINTHROP is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) of HAT due to *T. b. gambiense* in adults and children ≥6 years old and weighing ≥20 kg.
	Proposed: FEXINIDAZOLE WINTHROP is indicated for the treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* (g-HAT) and *Trypanosoma brucei rhodesiense* (r-HAT*)* in adults and children ≥6 years old and weighing ≥20 kg.
Dosage in the EEA	Current: Method of administration: *Oral use:* The use of FEXINIDAZOLE WINTHROP should be supervised by healthcare professionals trained in the management and treatment of patients with HAT.

Administration of FEXINIDAZOLE WINTHROP to all eligible patients should be done under the strict supervision of trained health staff, who needs to confirm that the patient is in fed condition and who directly observes each drug intake.

In patients where it is considered that the risk of poor compliance is low, outpatient administration should be done in hospitals or peripheral health facilities, and in particular situations, at home, but always under the strict supervision of trained health staff who ensures daily compliance of drug intake with food, for the total duration of treatment (10 days).

Posology:

FEXINIDAZOLE WINTHROP should be taken once daily for 10 days with food each day at about the same time of the day.

The table below shows the recommended dosage regimens for children from the age of 6 years and adults according to body weight.

Table 5a - Posology of FEXINIDAZOLE WINTHROP in adults and children

Body weight	Posology (number of 600 mg tablets) to be taken once daily with food	Duration of dose
≥35 kg		
Loading dose	1800 mg (3 tablets)	4 days
Maintenance dose	1200 mg (2 tablets)	6 days
≥20 and <35 kg		
Loading dose	1200 mg (2 tablets)	4 days
Maintenance dose	600 mg (1 tablet)	6 days

Missed dose:

If a dose is missed (not taken on the assigned day), normal dosing should resume the following day until the full course (10 days) of treatment has been completed. If a second dose is missed, the trained healthcare staff responsible of the treatment should decide how to continue the treatment based on the time point of occurrence within the scheduled dosing regimen.

Vomiting:

During the clinical trials, vomiting occurred after fexinidazole administration.

If a first event of vomiting occurs after receiving FEXINIDAZOLE WINTHROP, do not re-dose. Patient should take the next dose the following day using the recommended treatment schedule. Pharmacokinetic data from clinical trials have shown that this should not impact the efficacy of the treatment.

If a second event of vomiting occurs after administration of any other dose of FEXINIDAZOLE WINTHROP, the healthcare staff responsible of the treatment should decide how to continue the treatment based on the timing of the vomiting after administration and the occurrence of the event within the scheduled dosing regimen.

Proposed:

No updates proposed for human African trypanosomiasis (HAT) due to *T.b. rhodesiense* (r-HAT) indication.

Pharmaceutical form(s) and strength(s)	Current: Pharmaceutical form: Tablet. Each tablet contains 600 mg fexinidazole.
	Proposed: No updates proposed for human African trypanosomiasis (HAT) due to Trypanosoma brucei rhodesiense (r-HAT) indication.
Is/will the product (be) subject to additional monitoring in the EU?	Not applicable as Article 58 application.

ATC: Anatomical Therapeutic Chemical; eCTD: Electronic-Common Technical Document; EEA: European Economic Area; EU: European Union; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; INN: International Nonproprietary Name; PK: Pharmacokinetic; r-HAT: *Rhodesiense* Human African Trypanosomiasis; RMP: Risk Management Plan.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

FEXINIDAZOLE WINTHROP is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) of HAT due to *T.b. gambiense* in adults and children ≥6 years old and weighing ≥20 kg. FEXINIDAZOLE WINTHROP is proposed for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) of HAT due to *T. b. rhodesiense* in adults and children ≥6 years old and weighing ≥20 kg.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of the Human African Trypanosomiasis (HAT)

Indication	**Human African trypanosomiasis (HAT) due to *T. b. gambiense and T. b. rhodesiense***
Incidence	The aged-standardized incidence of HAT by IHME (including HAT due to *T. b. gambiense*, *T. b. rhodesiense* and to unspecified trypanosoma) was estimated in 2019 to 0.17 (95% CI [0.11 - 0.33]) per 100 000 person in Africa, and more specifically to 0.21 (95% CI [0.14 - 0.33]) in Sub-Saharan Africa. (1) Technical and logistical support to National Sleeping Sickness Control Programmes, improved access to diagnosis and treatment, better mapping and planning of control activities and increased support for the development of new drugs, diagnostics and epidemiological tools, all contributed to a substantial reduction in the annual number of cases reported. Cases of *gambiense* HAT (g-HAT) represent the main burden of the disease (ie, 98% of the total number of new cases reported), but in 2018 compared to 2000 their number decreased by 96%. (2) In the last 5 years, over 70% of reported cases occurred in the Democratic Republic of the Congo, with an average of less than 1000 cases declared annually. (3)(4) In 2021, 747 new cases of *T. b gambiense* and 55 of *T. b. rhodesiense* HAT (r-HAT) were reported to WHO.

Table 6a: Total number of new cases of *g*-HAT reported to WHO by disease endemic countries 2000-2021 (4)

Country	Years									
	2000	**2005**	**2010**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Angola	4546	1727	211	35	19	18	79	30	33	174
Benin	0	0	0	0	0	0	0	0	0	0
Burkina Faso	0	0	0	1	0	0	0	0	0	0
Cameroun	27	3	16	6	6	5	7	20	2	11
Chad	153	190	232	67	53	28	12	16	17	15
Central African Republic	988	666	395	147	124	76	57	86	39	44
Congo	111	398	87	36	18	15	24	17	15	18
Côte d'Ivoire	188	42	8	3	0	3	2	1	0	1

Indication	Human African trypanosomiasis (HAT) due to *T. b. gambiense and T. b. rhodesiense*

Democratic Republic of Congo	16 975	10 269	5629	2351	1769	1100	660	613	395	425
Equatorial Guinea	16	17	8	0	3	4	4	3	1	3
Gabon	45	53	22	9	10	9	16	8	11	18
Ghana	1	0	0	0	0	0	0	0	0	0
Guinea	52	94	68	29	107	139	74	69	36	28
Guinea Bissau	ND	ND	ND	ND	ND	0	ND	ND	ND	ND
Liberia	ND	ND	ND	ND	ND	ND	ND	ND	0	0
Mali	0	0	0	0	0	0	0	0	0	0
Nigeria	14	21	2	0	1	0	0	0	0	0
Sierra leone	0	0	0	0	0	ND	ND	ND	ND	ND
South Sudan[a]	1801	1853	199	45	17	12	17	11	15	10
Togo	0	0	0	0	0	0	0	0	0	0
Uganda	948	311	101	4	4	0	1	2	1	0
Total reported	25 865	15 644	6978	2733	2131	1409	953	876	565	747

a South Sudan became an independent state on 09-Jul-2009. All the cases reported up to that date in former Sudan correspond to the current South Sudan. Data for 2010, 2011 and 2012 include revisions of previously published figures.

No data available for Gambia, Guinea Bissau (except year 2017), Liberia (except years 2020-2021), Niger, and Senegal.

HAT: Human African Trypanosomiasis; g-HAT: *Gambiense* Human African Trypanosomiasis; ND: No Data; WHO: World Health Organization.

Table 6b: Total number of new cases of r-HAT reported to WHO by disease endemic countries 2000-2021 (5)

Country	Years									
	2000	**2005**	**2010**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Kenya	15	0	0	0	0	0	0	0	0	0
Malawi	35	41	29	30	35	7	15	91	89	49
Rwanda	ND	ND	ND	ND	0	0	0	0	0	0
United Republic of Tanzania	350	186	5	2	4	3	0	3	1	1
Uganda	300	473	112	28	10	13	4	5	2	2

Indication	**Human African trypanosomiasis (HAT) due to *T. b. gambiense and T. b. rhodesiense***
	<table><tr><td>Zambia</td><td>9</td><td>7</td><td>8</td><td>9</td><td>4</td><td>3</td><td>5</td><td>15</td><td>6</td><td>3</td></tr><tr><td>Zimbabwe</td><td>-</td><td>3</td><td>2</td><td>3</td><td>1</td><td>1</td><td>0</td><td>2</td><td>0</td><td>0</td></tr><tr><td>Total reported</td><td>709</td><td>710</td><td>156</td><td>72</td><td>54</td><td>27</td><td>24</td><td>116</td><td>98</td><td>55</td></tr></table> No data available for Botswana, Burundi, Eswatini, Ethiopia, Mozambique, Namibia, Rwanda (except since year 2016), Swaziland. HAT: Human African Trypanosomiasis; ND: No Data; r-HAT: *Rhodesiense* Human African Trypanosomiasis; WHO: World Health Organization. During the period 2016-2020, a total of 55 million people distributed over 120 000 km^2 are estimated to be at risk for HAT. Among those, 52 425 x 10^3 (95%) people were at risk of *T. b. gambiense* HAT and 2500 x 10^3 (5%) people at risk of *T. b rhodesiense*. Overall, only 6% of population at risk (ie, 3 million people) are considered at moderate or higher risk, compared with 11% for the period 2014-2018. (2)(6)
Prevalence	In 2019 the age-standardized prevalence of HAT in African continent was 0.31 (95% CI [0.13 - 0.63]) per 100 000 persons years and 0.39 (95% CI [0.17 - 0.80]) per 100 000 persons years in Sub-Saharan region. (1) A recent cross-sectional study carried out in Republic of Congo estimated the prevalence of HAT between Jun-2020 and Jan-2021 to 0.3%. In 2021, the *gambiense* form was reported in 11 endemic countries, with a total of 750 cases declared to the WHO. The number of declared cases was higher in regard to the 565 cases declared in 2020. This increase is in all likelihood due to increased case-finding activity, as systems get progressively back to normal after restrictions provoked by the COVID-19 pandemic. Of these cases, 57% were reported in the Democratic Republic of the Congo. (7) In 2021, a total of 55 cases of *rhodesiense* form were reported in four countries with almost 90% of cases occurring in Malawi. This overall figure shows a significant decrease with respect to 2020 data, when 98 cases were reported. (7) Although this is a slight increase on 2020 figures, the general trend continues and cases remain below 1000, the symbolic threshold achieved for the first time in 2018. (7) A 79% reduction of HAT diagnosed cases was observed worldwide between 2011 and 2020 (from 155 961 cases to 33 096). (6) During the period 2011-2020, 49 HAT cases were diagnosed and reported in 16 non-endemic countries, 35 (71%) cases were caused by the *rhodesiense* form of the disease and 14 (29%) cases by the *gambiense* form. Among those reported cases, 49% (24/49) were diagnosed in Europe, 22% (11/49) in one African non-DEC (South Africa), 14% (7/49) in North America, 12% (6/49) in Asia and one case in South America. In regard to the 2001-2010 period, this is corresponding to a 44% reduction of the number of reported cases. (8)
Demographics of the population in the authorized or proposed-indication	***Gambiense*** HAT is predominately a disease of adults. Age-specific prevalence rates peaked in the young-to-mid-adult range in most case finding surveys. Rates in children are usually less than half those in adults about 24% less than 15 years old, reflecting less exposure to flies during daily activities. The biggest existing comprehensive and accessible database of HAT treated cases is the one set up by MSF and maintained by Epicenter from 18 programmes in 6 African endemic countries the proportion of the all treated HAT population that were children aged <15 years was 23.7%, consisting of the following age subgroups: <5 years was 4.2%, ≥5 and <10 years was 6.6% and ≥10 and <15 years old was (12.8%) (Gerado Priotto, personal communication).The sex distribution depends on behavior and activities in specific epidemiological settings. In places where at-risk activities include mining, hunting and fishing, the prevalence of infection in males is greater than that in females; however, in transitional vegetation zones between forest and woodland, where infection is associated with cultivation and activities at water points, a similar prevalence of infection was found in males and females in case detection surveys. (9)

<table>
<tr><td>Indication</td><td>Human African trypanosomiasis (HAT) due to T. b. gambiense and T. b. rhodesiense</td></tr>
<tr><td></td><td>The age groups at highest risk for r-HAT are active, working-age groups who are most likely to venture to tsetse habitats and animal reservoirs, eg, to herd cattle or to farm in peripheral areas near to and to collect firewood, honey, to fish and hunt into, natural protected areas including the rangers working in. (9)</td></tr>
<tr><td>Main existing treatment options</td><td>The substances developed in the first half of the past century must be considered major developments in the treatment of a formerly 100% fatal disease, but all have major disadvantages: they are either highly toxic that can be lethal to approximately 5% to 8.5% of patients owing to post-treatment reactive encephalopathy (10) (melarsoprol) or are reasonably tolerable but do not sufficiently pass the blood-brain barrier (suramin, pentamidine), and their use is restricted to treatment of first-stage disease. (9)
In the 1980s, an antineoplastic drug, eflornithine, received attention for its antitrypanosomal activity, and the compound was eventually registered by the US Food and Drug Administration for this indication in 1990. Because its administration is highly complex, however, requiring sophisticated logistics and nursing care, and because of its high price, its use was limited for a long time to second line treatment or used by a few nongovernmental organizations that could afford its complex administration. In addition, eflornithine is not active against T. b. rhodesiense, which restricts the treatment options for the second-stage of this form of HAT to melarsoprol. At the same time as eflornithine was introduced, nifurtimox, which had been developed against Chagas disease, was used experimentally mainly to treat cases refractory to melarsoprol. The compound had only limited activity when used alone and it caused significant adverse reactions. (9) However, when nifurtimox is combined to eflornithine significantly reducing its monotherapy regime in time and dose while keeping same efficacy and safety.(10) In 2009, results from a pivotal clinical trial showed that NECT, a combined treatment of nifurtimox and eflornithine, was a safe and effective treatment for sleeping sickness (g-HAT). (10) Fexinidazole is an oral treatment for g-HAT. It was included in 2019 in the WHO Essential medicines list and WHO HAT treatment guidelines. This molecule is indicated as first line for first stage and non-severe second stage. New treatment guidelines for g-HAT were issued by WHO in 2019. In total six different drugs are used for the treatment of sleeping sickness. These drugs are donated to WHO by manufacturers and distributed free of charge to disease endemic countries. (11)
Table 6c: Treatment of HAT according to subspecies and stage of the disease (9)(12)(11)
<table>
<tr><th></th><th>First-stage</th><th>Second stage</th></tr>
<tr><td>T. b. rhodesiense</td><td>Suramin (IV)</td><td>Melarsoprol (IV)</td></tr>
<tr><td>T. b. gambiense</td><td>Pentamidine (IM) or (IV)</td><td>Eflornithine (IV) and nifurtimox (oral)</td></tr>
<tr><td></td><td>Fexinidazole (oral)</td><td>Eflornithine (IV)</td></tr>
<tr><td></td><td></td><td>Melarsoprol (IV)</td></tr>
<tr><td></td><td></td><td>Fexinidazole (oral)</td></tr>
</table>
IM: Intramuscular; IV: Intravenous; HAT: Human African Trypanosomiasis.</td></tr>
<tr><td>Natural history of the indicated condition in the untreated population including mortality and morbidity</td><td>Human African trypanosomiasis is almost always fatal if untreated or inadequately treated and is a substantial cause of both mortality and morbidity in affected regions. (9)
Following Tsetse fly bite, an immediate local reaction can be observed in about 50% of patients infected by T. b. rhodesiense, but more rarely with T. b gambiense (5% to 26%). (13)(14)
The HAT disease evolves in two stages after an incubation period. The incubation period lasts from a few days to several years for g-HAT, while the period is shorter (<3 weeks) for r-HAT.
The first stage of the disease (haemolymphatic stage) corresponds to the lymph and blood parasites dissemination (haematogenous and lymphatic dissemination). The second stage of the disease (meningoencephalitic stage) corresponds to the invasion of the central nervous system.
Gambiense HAT is characterized by a chronic progressive course that can last for several years. In absence of treatment, cachexia, lethargy, coma and death will occur for g-HAT. Rhodesiense</td></tr>
</table>

Indication	Human African trypanosomiasis (HAT) due to *T. b. gambiense and T. b. rhodesiense*
	HAT is an acute disease, which progress to second stage within a few weeks and to death mosltly because of myocarditis within 3 to 6 months. (13)
Important co-morbidities	• Patients with HAT tend to suffer from co-morbidities such as malnutrition, other parasitic infections (including malaria), tuberculosis and more susceptibility to viral and bacterial infections. However, literature is very limiting regarding the prevalence of such co-morbidities. The first comorbidity reported in patients with HAT is a co-infection with malaria. A recent meta-analysis estimated a pooled prevalence of malaria in patients with HAT to 50% (95% CI 28% to 78%, I^2 = 98.1%, seven studies). (15) Sub-group analysis by type of HAT (*gambiense* vs *rhodesiense* HAT) revealed that among patients with *g*-HAT the prevalence of malaria was 46% (95% CI 14% to 78%, I^2 = 96.62%, four studies) and 44% (95% CI = 40% to 49%, I2 = 98.3%, three studies) for patients with r-HAT. However, an important heterogeneity was observed with I^2 statistic greater than 50%.

CI: Confidence Interval; COVID-19: Coronavirus Disease; DEC: Disease Endemic Countries; HAT: Human African Trypanosomiasis; g-HAT: *Gambiense* Human African Trypanosomiasis; IHME: Institute for Health Metrics and Evaluation; IM: Intramuscular; IV: Intravenous; MSF: Médecins Sans Frontières/Doctors Without Borders; NECT: Nifurtimox-Eflornithine Combination Therapy; ND: No Data; r-HAT: *Rhodesiense* Human African Trypanosomiasis; WHO: World Health Organization; US: United States;

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Fexinidazole was evaluated in a battery of non-clinical safety pharmacology studies assessing central nervous, cardiovascular and respiratory systems, in a battery of general toxicity studies (single-dose studies in mice, rats, guinea-pigs and rabbits, and repeat-dose studies for up to 28 days and 3 months in rats and dogs - the two 28 day toxicity studies were conducted to Good Laboratory Practice (GLP) and are regarded as pivotal studies for risk assessment), in a comprehensive battery of genetic toxicology studies (including assessment of metabolites and impurities), in an in vitro assay for phototoxicity (both fexinidazole and its two main metabolites M1 and M2), in a male/female fertility study in rats, in embryo-fetal developmental toxicity studies in rats and rabbits, and in a pre/post-natal developmental toxicity study in rats. No carcinogenicity studies were conducted as fexinidazole is not intended to be used for more than 6 months nor repeatedly in an intermittent manner. Toxicokinetic analysis was included in the 28 day toxicity studies in rats and dogs, and in the reproductive and developmental toxicity studies in rats and rabbits, to enable correlation of fexinidazole, M1 and M2 plasma levels with toxicity.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • **Key issues identified from acute or repeat-dose toxicity studies** • Acute toxicity in the guinea pig and the rabbit with first lethal dose at 630 mg/kg and 1250 mg/kg, respectively, compared to 10 000 mg/kg in the mouse or in the rat.	Cause for death in these acute experiments was not identified. Higher toxicity in the rabbit and the guinea pig is presumably due to higher sensitivity of oral treatment with antimicrobials and resulting deterioration of gut flora in these 2 species. Dose levels showing acute toxicity were substantially beyond intended clinical doses.
Reduction in food consumption and bodyweight were observed at high doses throughout repeat dose studies in both the rat and the dog. The finding was showed to be reversible.	Those changes occurred in the absence of identified target organ toxicity, as it is usually the case when secondary to overt toxicity. Potential central effect on feeding behavior and satiety cannot be excluded, therefore. Animal studies were conducted in young and still developing adults which tends to exaggerate effect on bodyweight. Relevance to humans remains equivocal. Comments: As a key non-clinical safety finding, reduction in food consumption and body weight is considered as an important potential risk. Nevertheless, bodyweight loss and reduced feed behavior has not been identified as a limiting effect of fexinidazole in the clinic. Besides, the effect is seen at high doses only and is reversible. Risk appears to be limited, therefore.
Minimal to slight increased liver weight with hypertrophy of centrilobular hepatocytes at histology were observed in the rat after repeat high doses. They were associated with minimal increases in liver parameters.	These changes are common adaptive/reversible changes in the rat, not relevant to humans.

Key Safety Findings	Relevance to human usage
Reproductive/developmental toxicity studies: Fexinidazole showed no effect on fertility, pregnancy and no direct effect on prenatal development but elicited slight growth inhibition throughout lactation and post weaning period up to maturity for F1 rat pups at 600 mg/kg/day. This retardation of growth slightly retarded sexual maturation of animals at that dose.	This finding is potentially relevant to human, although limited to high dose level. Comments: As non-clinical key safety finding, growth retardation and delay in sexual maturity in suckling pups is considered as an important potential risk. Effect is likely to be due either to exposure of pups to fexinidazole through milk, or reduction in milk production by the dams exposed to toxic dose levels. Risk appears to be limited as the effect is a developmental delay, not organ toxicity, does not translate into any functional impairment and is likely to be reversible.
• **Genotoxicity** • Positive results in Ames tests with fexinidazole, and M1 and M2 metabolites.	Nitroso compounds commonly show positive results in bacterial tests which are attributed to reduction through bacterial nitroreductase. These results are generally regarded as not extrapolable to humans. As further evidence for non-relevance, tests in nitroreductase-deficient bacteria and in mammalian cells were negative.
Safety pharmacology There was no key safety findings in central nervous system, respiratory nor cardiovascular testing with fexinidazole. Weak inhibition of hERG channel at high M2 concentration (30 μM) did not translate into any ECG signal in the dog.	Potential M2 effect on K^+ channel may translate into QT prolongation in human.
Other toxicity-related information or data M1 and M2 metabolites of fexinidazole carry a signal for phototoxicity in the 3T3 test at high concentrations. Tissue distribution studies performed with radio labelled fexinidazole at 800 mg/kg in albino and pigmented rats showed no evidence for accumulation of radioactivity in the skin or in the eyes, and a similar affinity for both pigmented and non-pigmented skin.	There is a potential for phototoxicity reactions in patients treated with fexinidazole and exposed to sunlight or artificial UV-A light. However, based on distribution studies the risk to patients is regarded as low. Comments: As non-clinical key safety finding, phototoxicity is considered as an important potential risk. In relation to HAT patients the effect was not observed.

ECG: Electrocardiogram; HAT: Human African trypanosomiasis; hERG: human Ether-a-go-go-Related Gene; UV-A: Ultraviolet-A.

No pre-clinical toxicology study in juvenile animals has been conducted to cover the pediatric use of fexinidazole. Nevertheless, the GLP general toxicology studies in the rat and the dog, which were conducted in immature animals based on their age at study initiation, and/or microscopy of sexual organs at necropsy, did not show any toxicity that would differ in young mammals or affect their long-term development. Further, there were no pre and/or post-natal developmental findings in the GLP Segment I, II and III reprotoxicity studies, other than slight, reversible developmental delays. In addition, the results from in vitro metabolism studies using hepatocytes or liver microsomes from juvenile rats and dogs were similar to those from adult animals.

Overall, and considering the long experience of using 5-nitroimidazole compounds as anti-infective drugs in humans, including clinical data already gathered with fexinidazole, it is considered unlikely that additional preclinical juvenile data would enhance further our understanding of the

potential risks of using fexinidazole in the pediatric population, nor that any finding would offset clinical benefit in this population.

Conclusion from the key safety findings:

On the basis of these non-clinical findings, the use of fexinidazole during pregnancy/lactation is considered as missing information listed into [Module Part II SVIII].

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Clinical Trial Exposure:

Table 8 - Duration of exposure

Duration of exposure (at least)	Patients
<10 days	936 (100%)
10 days	858 (91.7%)
≥11 days	261 (27.9%)
Total person	**936**

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT; Visceral Leishmaniasis study: DNDiFEXIVL001; and Chagas studies: DNDi-CH-FEXI-001 and DNDi-FEX-12-CH.
HAT: Human African Trypanosomiasis.

Table 9 - Duration of exposure and by indication

Duration of exposure (at least)	Patients (N = 936)
***Gambiense* Human African Trypanosomiasis (HAT)**	
<10 days	793 (100%)
10 days	758 (95.6%)
≥11 days	234 (29.5%)
Total person	**793**
***Rhodesiense* HAT**	
<10 days	45 (100%)
10 days	44 (97.8%)
>10 days	0
Total person	**45**
Visceral Leishmaniasis	
<10 days	14 (100%)
10 days	14 (100%)
≥11 days	0
Total person	**14**
Chagas	
<10 days	84 (100%)
10 days	42 (50.0%)
≥11 days	27 (32.1%)
Total person	**84**

Duration of exposure (at least)	Patients (N = 936)

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT; Visceral Leishmaniasis study: DNDiFEXIVL001; and Chagas studies: DNDi-CH-FEXI-001 and DNDi-FEX-12CH.
HAT: Human African Trypanosomiasis.

Table 10 - Exposure by age group and gender

	Patients (N = 936)	
Total population	**Male (N = 487)**	**Female (N = 449)**
≥6 to <15 years	101(20.7%)	91 (20.3%)
≥15 to <18 years	38 (7.8%)	42 (9.4%)
≥18 to <50 years	297 (61.0%)	264 (58.8%)
≥50 to <65 years	42 (8.6%)	44 (9.8%)
≥65 years	9 (1.8%)	8 (1.8%)
Total	**487**	**449**

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT; Visceral Leishmaniasis study: DNDiFEXIVL001; and Chagas studies: DNDi-CH-FEXI-001 and DNDi-FEX-12-CH.
HAT: Human African Trypanosomiasis.

Table 11 - Exposure by age group and gender and by indication

	Patients (N = 936)	
Total population	**Male (N = 487)**	**Female (N = 449)**
Human African Trypanosomiasis (HAT)		
***Gambiense* HAT**		
≥6 to <15 years	94 (22.3%)	86 (23.1%)
≥15 to <18 years	32 (7.6%)	42 (11.3%)
≥18 to <50 years	250 (59.4%)	196 (52.7%)
≥50 to <65 years	37 (8.8%)	41 (11.0%)
≥65 years	8 (1.9%)	7 (1.9%)
Total	421	372
***Rhodesiense* HAT**		
≥6 to <15 years	7 (22.5%)	5 (35.7%)
≥15 to <18 years	5 (16.1%)	0 (0%)
≥18 to <50 years	16 (51.6%)	8 (57.1%)

	Patients (N = 936)	
≥50 to <65 years	2 (6.4%)	0 (0%)
≥65 years	1 (3.2%)	1 (7.1%)
Total	**31**	**14**
Visceral Leishmaniasis		
≥15 to <18 years	1 (7.7%)	0
≥18 to <50 years	11 (84.6%)	1 (100%)
≥50 to <65 years	1 (7.7%)	0
Total	**13**	**1**
Chagas		
≥15 to <18 years	0	0
≥18 to <50 years	20 (90.9%)	59 (95.2%)
≥50 to <65 years	2 (9.1%)	3 (4.8%)
Total	**22**	**62**

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT; Visceral Leishmaniasis study: DNDiFEXIVL001; and Chagas studies: DNDi-CH-FEXI-001 and DNDi-FEX-12-CH.

HAT: Human African Trypanosomiasis.

Table 12 - Exposure by dose

Total	Patients (N = 936)
1200 mg/d for 4 days followed by 600 mg/d for 6 days	171 (18.2%)
1800 mg/d for 4 days followed by 1200 mg/d for 6 days	681 (72.7%)
1800 mg/d for 8 weeks	7 (0.7%)
1800 mg/d for 4 weeks	6 (0.6%)
1800 mg/d for 2 weeks	7 (0.7%)
1200 mg/d for 8 weeks	7 (0.7%)
1200 mg/d for 4 weeks	7 (0.7%)
1200 mg/d for 2 weeks	6 (0.6%)
600 mg/d for 10 days	14 (1.4%)
1200 mg/d for 3 days	15 (1.6%)
600 mg/d for 3 days followed by 1200 mg/d for 4 days	15 (1.6%)
Total	**936**

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT; Visceral Leishmaniasis study: DNDiFEXIVL001; and Chagas studies: DNDi-CH-FEXI-001 and DNDi-FEX-12-CH.

HAT: Human African Trypanosomiasis.

Table 13 - Exposure by dose and by indication

Total population	Patients (N = 936)
Human African Trypanosomiasis (HAT)	
***Gambiense* HAT**	
1200 mg/d for 4 days followed by 600 mg/d for 6 days	160 (20.2%)
1800 mg/d for 4 days followed by 1200 mg/d for 6 days	633 (79.8%)
Total	**793**
***Rhodesiense* HAT**	
1200 mg/d for 4 days followed by 600 mg/d for 6 days	11 (24.4%)
1800 mg/d for 4 days followed by 1200 mg/d for 6 days	34 (75.6%)
Total	**45**
Visceral Leishmaniasis	
1800 mg/d for 4 days followed by 1200 mg/d for 6 days	14 (100%)
Total	**14**
Chagas	
1800 mg/d for 8 weeks	7 (8.3%)
1800 mg/d for 4 weeks	6 (7.1%)
1800 mg/d for 2 weeks	7 (8.3%)
1200 mg/d for 8 weeks	7 (8.3%)
1200 mg/d for 4 weeks	7 (8.3%)
1200 mg/d for 2 weeks	6 (7.1%)
600 mg/d for 10 days	14 (16.6%)
1200 mg/d for 3 days	15 (17.9%)
600 mg/d for 3 days followed by 1200 mg/d for 14 days	15 (17.9%)
Total	**84**

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT; Visceral Leishmaniasis study: DNDiFEXIVL001; and Chagas studies: DNDi-CH-FEXI-001 and DNDi-FEX-12-CH.
HAT: Human African Trypanosomiasis.

Table 14 - Exposure by HAT stage

Human African Trypanosomiasis (HAT)	Patients (N = 838)
***Gambiense* HAT**	
First Stage	301 (38.0%)
Early Stage 2	87 (11.0%)
Late Stage 2	405 (51.1%)
Total	**793**

Human African Trypanosomiasis (HAT)	Patients (N = 838)
***Rhodesiense* HAT**	
Stage-1 r-HAT	10 (22%)
Early Stage-2 r-HAT	1 (2.2%)
Stage-2 r-HAT	34 (75.6%)
Total	**45**

For study DNDIFEX004, stage of disease is defined by protocol.

Studies included: *Gambiense* HAT studies: DNDiFex004, DNDiHATFEX005, DNDiHATFEX006, DNDi FEX 09 HAT; *Rhodesiense* HAT study: DNDi FEX-07-HAT.

HAT: Human African Trypanosomiasis; r-HAT: *Rhodesiense* Human African Trypanosomiasis.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 15 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypersensitivity to fexinidazole and/or to any nitroimidazole drugs	Hypersensitivity may be potentially severe/ serious and might interfere with the evaluation of study medication.	No	The use of fexinidazole is contraindicated in case of hypersensitivity to fexinidazole and/or to any nitroimidazole drugs.
Children <6 years old or weighing less than 20 kg	Clinical program limited to adults and children above 6 years old, due to the size of the tablet.	Yes	
Children <6 years old weighing 20 kg or more	Population not included in CT clinical program limited to adults and children above 6 years old, due to the size of the tablet.	No	No reason to anticipate any safety issue as metabolism would not be different from a 6 years old - probability of a HAT child of <6 years with weight ≥25 is low based on existing data from excluded patients in DNDiFEX006.
Patients with severe hepatic impairment	Might interfere with the evaluation of study medication.	No	Hepatotoxicity is considered as an important potential risk. The use of fexinidazole is contraindicated in case of clinical signs of cirrhosis or in jaundice.
• Laboratory abnormalities, clinically significant such as AST and ALT ≥2 ULN[a] • Total Bilirubin >1.5 ULN • Severe Leucopenia (<2000/mm3)	Might interfere with the evaluation of study medication.	No	Hepatotoxicity is considered as an important potential risk. Severe infection secondary to drug-induced neutropenia is considered as an important potential risk.
Pregnancy/Lactation[b]	Absence of safety data in these populations.	Yes	-

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
QTcF ≥450 msec[a]	Might interfere with the evaluation of study medication.	No	Proarrhythmic effect is considered as important potential risk.

a Not considered as exclusion criteria in FEX007 study.

b In FEX007 and FEX009 studies, 2nd and 3rd trimester pregnant patients and breastfeeding patients were included.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; HAT: Human African Trypanosomiasis; QTcF: Corrected QT Interval by Fridericia; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme can detect adverse drug reactions (ADRs) that are uncommon (≥1/1000 to <1/100) or more frequent. Indeed, with approximately 838 HAT patients (including g-HAT and r-HAT) exposed in the Phase 2/3 clinical program, the probability to observe at least one occurrence of an adverse event (AE) in the fexinidazole group is 95%, if this event truly occurs in at least 0.48% of the population. Cumulative effects are not anticipated due to the short half-life of fexinidazole, extensive metabolism and lack of accumulation shown on repeat dosing. In addition, no cumulative effects are expected from the metabolites, M1 and M2, as their C_{max} showed no increase on repeat dosing following dose reduction (to maintenance dose) under the clinical dosing scheme, and they showed no affinity for any specific tissues eg, melanin containing tissues. Further, due to a short half-life, the M1 metabolite showed little potential for accumulation over time.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 16 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant women in the second or third trimester (5 female patients were included and exposed to fexinidazole while being pregnant in the second or third trimester in the DNDi-FEX-09-HAT (n = 4) and DNDi-FEX-07-HAT (n = 1) studies).
Breastfeeding women	Breastfeeding women (17 female patients were included and exposed to fexinidazole while the child was breastfed during the 10 days of study treatment of the patient in the DNDi-FEX-09-HAT study).
• Patients with relevant comorbidities • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment/ known history or	Not included in the clinical development program.

Type of special population	Exposure
evidence of clinically significant cardiac rhythm disorders • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	
Populations with relevant different ethnic origin	Amerindians (40 patients were exposed to fexinidazole in the CHAGAS study DNDi-CH-FEXI-001). Hispanic (44 patients were exposed to fexinidazole in CHAGAS study DNDi-FEX-12-CH)
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable
Other Patients with Cockayne Syndrome	Not included in the clinical development program.

Conclusion:

Very limited (n=5) data are available concerning the use of fexinidazole in pregnant women in the second or third trimester and no data are available in pregnant women in the first trimester which are part of the target populations (g-HAT and r-HAT). Therefore, the use of fexinidazole in pregnant women is considered as missing information.

Limited data are available concerning the use of fexinidazole in breast feeding women (with g-HAT; no case in r-HAT) which are part of the target population. Therefore, the use of fexinidazole in breast-feeding women is considered as missing information.

No data are available in the use of fexinidazole in patients with mild/moderate hepatic impairment. However, its use in patients with clinical signs of cirrhosis or jaundice is contraindicated. Therefore, hepatotoxicity is considered as important potential risk.

No adjustment in dosing of fexinidazole is required in patients with renal impairment, therefore its use in this population is not considered as a safety concern.

No data are available concerning the use of fexinidazole in patients with known history or evidence of clinically significant cardiac rhythm disorders. Pro-arrhythmic effect is considered as important potential risk.

In vitro, both the intrinsic clearance and the metabolite profile of fexinidazole were similar for hepatocytes from African American and Caucasian donors. Therefore, the use of fexinidazole in black sub-Saharan populations for treatment of HAT is not considered to pose additional safety concerns due to potential differences in metabolism.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

No sales data is made available, given fexinidazole is provided for free.

FEXINIDAZOLE WINTHROP Marketing Authorization (MA) was first granted in the Democratic Republic of Congo (DRC) on 24 December 2018 and the distribution started in DRC in January 2020 (first patient treated in DRC on 28 January 2020). FEXINIDAZOLE WINTHROP got authorization in US on 16 July 2021 and Uganda on 05 October 2021. In addition, fexinidazole is currently distributed by the WHO in the remaining g-HAT endemic countries (Angola, Burkina Faso, Cameroon, Congo, Central African Republic, Chad, Equatorial Guinea, Gabon, Guinea and South Soudan).

Public Health Program (PHP) was implemented by the National Sleeping Sickness Control Program (NSSCP) as per WHO interim guidelines 2019 (WHO interim guidelines for the treatment of HAT version May 2019). Two hundred and fifty six (256) subjects with g-HAT have been exposed to fexinidazole in the WHO implementation up to 30 September 2022 (Table 17).

Table 17 - Fexinidazole Periodic Report - Cumulative data as of 30-Sep-2022

		Missing Value (N or %)
[redacted]		
Number of patients reported	256	
Sex ratio (Male:Female)	1.02 (129:127)	
Age in years (median, range)	28 (7-79)	
Pregnant women	1	9
Trypanosomes seen (ratio T+:T0)	20.25 (243:12)	
Dosage prescribed (24tb:L, 14tb:S)	(205:49)	1
Full dosage given	247 (97%)	1
Any AE during treatment	173	
Serious AE during treatment	3	

		Missing Value (N or %)
Follow-up reports		
6 months	145	
12 months	86	
18 months	27	
24 months	1	
Unschedules	3	
Serious AE during follow-up	4	
Relapses	0	
Pregnancy outcome reports		
Termination, any cause	0	
Complications of labor/deliver	0	
Congenital anomaly	0	
Neonate death	0	
AE during the first 2 years of life		
Forms for children's AE filled	0	

AE: Adverse Event; [redacted] N: Number.

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

The potential for misuse of fexinidazole is considered unlikely because of its distribution modalities (controlled distribution restricting availability of fexinidazole in hospitals and specialized treatment centers) and a risk of dependence potential and abuse liability considered low on the basis of non-clinical data and clinical review:

- Tanimoto index below 0.32, the chemical structure of fexinidazole and its 2 metabolites do not present significant structural similarities with the chemical structures of representative known drugs of abuse such as morphine derivatives, central nervous system (CNS) stimulants, hallucinogenic compounds, benzodiazepines, cannabinoids or nicotine compounds.
- In repeat dose toxicological studies with fexinidazole in rats and dogs (from 7 days to up to 3 months), there were no clinical signs indicative of a potential drug dependence or abuse during the dosing periods, and when the administrations were stopped there was no evidence of spontaneous withdrawal signs during the recovery periods.
- The available safety data from Phase-I and Phase-II/III studies, examined using dedicated pre-specified Medical Dictionary for Regulatory Activities (MedDRA) queries, did not yield events raising a concern of drug dependence or abuse. Indeed, treatment emergent adverse events related to Drug abuse liability assessment (DALA) events in healthy subjects and in patients with fexinidazole were mostly unspecific, of moderate to mild intensity and of low frequency. They did not differ from those expected due to the disease and/or to the 5 nitroimidazole family of products. Moreover, the absence of any rebound or withdrawal effects across studies further supports the low risk of abuse and dependence potential for fexinidazole.

Therefore, given the data demonstrating lack of abuse liability and the planned controlled distribution system, reducing the potential risk of product diversion for any off label or drug abuse use, the sponsor is considering the risk of misuse negligible for fexinidazole and no risks to the public health as a result of misuse are anticipated.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics will be discussed in this Section and will be presented in Section SVII.1.1 (if the risks are not considered important for inclusion in the list of safety concerns in the RMP) or in Section SVII.1.2 (it the risks are considered important for inclusion in the list of safety concerns in the RMP):

- Potential harm from overdose
- Potential for risks resulting from medication errors
- Potential for transmission of infectious agents
- Potential for off-label use
- Pharmacological class effect common to other members of the pharmacological class not thought to be an important identified or potential risk with fexinidazole
- Important risk related to identified or potential pharmacokinetic and pharmacodynamic interactions
- Risk in pregnant and lactating women
- Effect on fertility
- Risks associated with the disposal of the used product
- Risks related to the administration procedure
- Pediatric safety issues

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)**
  - Potential harm from overdose:

It should be noted that higher doses of fexinidazole than the recommended clinical dosing in the HAT population were administered in the clinical pharmacology studies DNDiFEX001 Part I, DNDiFEX001 Part III and DNDiFEX003.

In Study DNDiFEX001 Part III, at the highest dose level of 3600 mg (repeated dose for 14 days in fasting conditions), fexinidazole was well tolerated. One subject [redacted] in the highest dose group experienced a peak increase in liver enzymes (aspartate aminotransferase [AST] 38.2 x upper limit

of normal [ULN] and alanine aminotransferase [ALT] 28.3 x ULN) after last dosing with a rapid return to normalization without treatment. All complementary exploration could not explain this sudden increase in liver function tests (LFT) for that subject, therefore for safety reason and in the light of the explanation available at that time it was decided not to expose other subjects on fexinidazole administration. The last subject under dosing (placebo) was also stopped as he showed some slight increase in LFT.

In Study DNDiFEX003 administering fexinidazole either 1800 mg or 2400 mg from Day 1 to 4, then 1200 mg from Day 5 to 10: In Cohort 1 (1800 mg then 1200 mg) 1 subject withdrew due an AE of vomiting after Day 3. In Cohort 2 (2400 mg then 1200 mg), 2 subjects withdrew due to AEs of vomiting on Day 3 and panic attack on Day 5. This led to the decision to not expose more healthy subjects to this dose level and to stop the study progression.

A pediatric patient in DNDiFEX006 received the higher dosing regimen (1800/1200 mg) instead of the lower dosing regimen (1200/600 mg) as adjusted for their weight as per protocol. At inclusion the patient presented with HAT symptoms of headache, pruritus and weight loss; blood potassium and calcium were normal, and albumin was just below normal levels. The patient experienced Treatment Emergent Adverse Events (TEAEs) of vomiting over the first 5 days of treatment and increased potassium and decreased calcium levels were observed from Day 11 to Week 9. The profile of TEAEs in this patient was therefore consistent with those observed in patients who received the higher dose of fexinidazole.

No further cases of overdose have been reported in HAT clinical trials. Due to the saturable dose response model, the maximal effect of about 30 ms calculated for QTcF is not expected to be increased in case of overdose, in average at the population level. In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. White blood cell (WBC) and transaminases (AST and ALT) should be monitored.

For each daily administration, patients will take 2 then 1 or 3 then 2 tablets (depending on his/her age). Each tablet containing 600 mg active substance is a 900 mg tablet size, which may not be attractive for a voluntary overdose.

Administration supervision is encouraged by national HAT programs, to ensure compliance to treatment. This will be ensured by a trained health care professional or by a trained accompanying person.

The potential for abuse is considered low, no misuse for recreational purpose is expected as per DALA assessment.

For these different reasons the overdose seems unlikely for fexinidazole, and therefore harm from overdose is not considered as a safety concern.

- Potential for risks resulting from medication errors:

No special concern has been identified regarding the usual administration of fexinidazole. Therefore, medication error is not considered as a safety concern.

- Potential for transmission of infectious agents:

Lactose monohydrate is the only animal origin excipient used in Fexinidazole tablets. The lactose supplier, DFE Pharma, certifies that the milk used to manufacture pharmaceutical grade lactose is sourced from healthy animals under the same conditions as milk collected for human consumption. The calf rennet used for production of the raw material whey is in accordance with European Medicines Agency (EMA) public statement EMEA/CPMP/571/02; milk hygiene directive 92/46/EEC). No ruminant materials other than calf rennet have been used to manufacture pharmaceutical grade lactose.

Therefore, there is no risk for transmission of infectious agents.

- Potential for off-label use:

The risk of using fexinidazole off-label in children below 6 years or less than 20 kg, or in other parasitic disease is considered low as the modalities for the distribution of fexinidazole to the endemic countries ie, control access program and controlled distribution system supervised by the NSSCPs in collaboration with WHO make the diversion of the drug unlikely (See [RMP Part V]).

Therefore, the potential for off-label use is not considered as an important risk.

- Pharmacological class effect common to other members of the pharmacological class not thought to be an important identified or potential risk with fexinidazole:

Products of similar class to fexinidazole, such as metronidazole and tinidazole have been associated with side effects including nephrotoxicity, metallic taste, dry mouth, facial/drug eruption, skin rash, and even Stevens-Johnson syndrome. Cutaneous reactions including rash have also been observed with benznidazole. Less than 1% of drug related pruritus were observed in the HAT clinical program. In Chagas disease study, skin hyperpigmentation was reported in 10 patients (25%) and were considered related to study drug. None were classed as serious. No other signs of phototoxicity occurred frequently in Chagas disease patients. Hyperpigmentation and signs of phototoxicity did not commonly occur in the HAT or visceral leishmaniosis (VL) studies.

- Effect on fertility:

A fertility study conducted up to the oral dose of 600 mg/kg in the male and female rats failed to identify any effect of fexinidazole on neither fertility nor reproductive performance.

- Risks associated with the disposal of the used product:

Not applicable

- Risks related to the administration procedure:

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 18 - Important identified risk considered for inclusion in the list of safety concerns: Psychiatric events

Psychiatric events[a]	
Scientific evidence that has led to the inclusion	Nitroimidazole Class effect. Clinical data HAT indication showed higher incidence (32% patients versus 18% NECT) of psychiatric related events including insomnia, psychotic symptoms, depression, anxiety. Of the psychiatric events occurring in fexinidazole administered HAT patients, 5 were considered by investigators and/or the sponsor to be serious; 2 cases of personality change and one case each of acute psychosis, psychotic disorder and suicidal ideation; 4 of these events occurred in study DNDiFEX004. In the Chagas Disease study, where patients were administered higher cumulative doses than were administered in HAT studies, insomnia was also seen very commonly (45.0%), as was depression (37.5%). One case of depression was considered serious and ended in suicide.
Risk-benefit impact	A serious psychiatric event can be life-threatening and result in death.

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety.
HAT: Human African Trypanosomiasis; NECT: Nifurtimox-Eflornithine Combination Therapy.

Table 19 - Important potential risk considered for inclusion in the list of safety concerns: Vomiting

Vomiting	
Scientific evidence that has led to the inclusion	Nitroimidazole Class effect. Clinical data in HAT indication showed high incidence of vomiting, 42% in pooled FEXI studies, while vomiting/emesis are not features of the HAT diseases itself. There was a trend to increased incidence of vomiting during the loading phase. Higher incidence in children (69%) in FEX006 study. In most fexinidazole patients, re-treatment after vomiting was only administered once and, thus vomiting did not have a clinically meaningful impact on efficacy or safety. Of note, vomiting has not led to treatment discontinuation. Overall, vomiting was of limited severity and duration.
Risk-benefit impact	Vomiting may be severe and repeated episodes may impact completed treatment cure.

HAT: Human African Trypanosomiasis.

Table 20 - Important potential risk considered for inclusion in the list of safety concerns: Pro-arrhythmic effect

Pro-arrhythmic effect	
Scientific evidence that has led to the inclusion	In both healthy subjects and patients, administration of fexinidazole resulted in an increase in QTcF of about 20 ms. The concentration-response analyses indicated that this increase in QTcF is most likely caused by metabolite fexinidazole sulfone M2 and not by fexinidazole or metabolite M1, which is consistent with results obtained in the in vitro hERG study. Two occurrences of treatment emergent QTc values (a biomarker of pro-arrhythmic effect) greater than 500 ms were documented during the pivotal study in HAT patients about 10 days after last fexinidazole administration, ie,

Pro-arrhythmic effect	
	when M2 concentrations are expected to be near baseline levels. There were no TEAEs suggesting a life-threatening ventricular arrhythmia, nor TdP reported during the development programme. Although the total number of treated subject is small, QTc increase is a biomarker of a pro-arrhythmia effect which can lead to cardiac arrhythmia or ultimately TdP. Given that a QTc prolongation may induce a cardiac arrhythmia, in absence of clinical evidence in patients treated with fexinidazole, the pro-arrhythmia effect is considered as a safety concern.
Risk-benefit impact	Cardiac arrhythmia and TdP may be life threatening and result in sudden death.

HAT: Human African Trypanosomiasis; hERG: human Ether-a-go-go-Related Gene; TEAE: Treatment Emergent Adverse Event; TdP: Torsades de pointes.

Table 21 - Important potential risk considered for inclusion in the list of safety concerns: Severe infection secondary to drug-induced neutropenia

Severe infection secondary to drug-induced neutropenia	
Scientific evidence that has led to the inclusion	No case of infectious complication was reported in patients treated with fexinidazole in the clinical studies, however severe infection is considered as an important potential risk based on the following clinical data: • Eight cases of severe neutropenia (Grade 3-4) were reported as serious adverse events in CHAGAS Bolivian patients treated with fexinidazole (out of 40 patients). These cases were asymptomatic and spontaneously reversible within 1 week. • Four HAT patients treated with fexinidazole (out of 619 patients) presented a non-serious related case of neutropenia and none was associated with any infectious complication. Analysis of patients with infection also showed no association with neutropenia.
Risk-benefit impact	Severe infection may be life-threatening and leading to death.

HAT: Human African Trypanosomiasis.

Table 22 - Important potential risk considered for inclusion in the list of safety concerns: Hepatotoxicity

Hepatotoxicity	
Scientific evidence that has led to the inclusion	• Nitroimidazole class effect. • No case of hepatotoxicity was reported form the clinical studies. However reversible increase in transaminase was observed in some patients treated with fexinidazole in the clinical studies: • In Chagas disease study 40% of patients experienced chronic or acute increase in ALT or AST >3 x ULN (versus none in the placebo arm). These observations were reversible, and no Hy's law cases were reported. No clinically significant increase in transaminase was reported in HAT patients treated with fexinidazole. • PK/PD analysis supports difference between HAT and Chagas. Fexinidazole showed no clinically evident drug-induced hepatic injury in HAT patients. • Based on the above, the applicant considers that hepatotoxicity risk in HAT cannot be excluded even if the risk is lower in HAT than in Chagas disease.
Risk-benefit impact	Hepatotoxicity can range from mild to fulminant hepatic failure resulting in death.

ALT: Alanine Aminotransferase; AST: Aspartate Transaminase; HAT: Human African Trypanosomiasis; PD: Pharmacodynamic; PK: Pharmacokinetic; ULN: Upper Limit of Normal.

Table 23 - Important potential risk considered for inclusion in the list of safety concerns: Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2 and CYP2C19

Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2 and CYP2C19	
Scientific evidence that has led to the inclusion	In vitro interaction study (Evidence source: Synexis 063-10 study) has shown that fexinidazole and the M1 metabolite can inhibit CYP1A2 and/or CYP2C19, leading to risk of DDI. Potential identified interaction: Fexinidazole could potentially increase the exposures of drugs metabolized mainly by CYP1A2 (such as caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline) or CYP2C19 (such as omeprazole, diazepam, mephenytoin).
Risk-benefit impact	As the M2 metabolite, which gives by far the highest and most prolonged exposure in man following treatment with fexinidazole, showed no inhibition of any tested CYPs, the risk for a DDI with clinical consequences is considered to be very low. However, the risk is to be investigated in a future clinical interaction study, studying the effects of fexinidazole treatment on the pharmacokinetics of the probes caffeine (marker for CYP1A2) and omeprazole (marker for CYP2C19).

CYP: Cytochrome P450; DDI: Drug-Drug Interaction.

Table 24 - Important potential risk considered for inclusion in the list of safety concerns-Development of resistance to fexinidazole, cross resistance between fexinidazole and nifurtimox

Development of resistance to fexinidazole, cross resistance between fexinidazole and nifurtimox	
Scientific evidence that has led to the inclusion	Fexinidazole has shown cross-resistance in in vitro and in vivo studies using a nifurtimox-resistant *T. b. gambiense*, suggesting a common mode of resistance and action amongst nitro drugs based on the MoA of parasite killing. Whilst it is unlikely, the potential for the development of resistance to fexinidazole or to NECT (used as rescue treatment) in HAT patients failing to respond to fexinidazole cannot be fully discounted.
Risk-benefit-impact	Impact on the benefit risk ratio of fexinidazole or NECT in HAT patients. Risk of disease progression

HAT: Human African Trypanosomiasis; MoA: Mechanism of Action; NECT: Nifurtimox-Eflornithine Combination Therapy.

Table 25 - Missing information considered for inclusion in the list of safety concerns: Use in pregnancy/lactation

Use in pregnancy/lactation	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Animal studies: In animals, effects of fexinidazole on embryo-fetal development were observed only at doses harmful to the dams. These effects were considered as secondary to maternal toxicity. Plasma concentrations of Fexinidazole and of its metabolites at these dose levels were low as compared to clinical exposures. (see [RMP Part II SII]). There are no data on exposure during pregnancy in human. (see [RMP Part II SIV]). There are limited data cases of exposure before pregnancy. There are no data from the use of fexinidazole in breast-feeding women. Fexinidazole, M1 and M2 metabolites are excreted in the milk when administered to lactating rats. Effects on suckling rat pups were limited to transient growth retardation at high dose level only.
Risk-benefit impact	As the targeted population of the indication should include women of childbearing potential and lactating women, the use of fexinidazole in pregnant or breast-feeding women is considered as missing information.

RMP: Risk Management Plan.

Table 26 - Missing information considered for inclusion in the list of safety concerns: Use in children <6 years old or less than 20 kg

Use in children <6 years old or less than 20 kg	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Application for fexinidazole is being submitted in EU according to the Art 58 procedure for which a PIP is not required. Therefore, no PIP has been performed. The safety and efficacy of fexinidazole have not been established in children less than 6 years of age or less than 20 kg in body weight.
Risk-benefit impact	As no data are available for the use of fexinidazole in these populations, its use in these populations may have an impact on the benefit risk ratio.

EU: European Union; PIP: Pediatric Investigation Plan.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

The following changes or reclassification are introduced in RMP v3.0:

- Case reports and literature reviews support an association between systemic use of metronidazole and irreversible hepatotoxicity/acute liver failure with fatal outcomes in patients with CS. Food and Drug Administration thus determined that nitroimidazole products (including Fexinidazole) represent a class of products that have the potential for the same serious risk of acute liver failure in patients with CS and requested the update of Fexinidazole United States Prescribing Information (USPI) (as well as those for products in the same class) to reflect the class effect. Sanofi reviewed available evidence on this risk. Based on review of the Sanofi global Pharmacovigilance (PV) database, worldwide scientific literature, main reference PV textbooks, and biological plausibility of metronidazole, the available cumulative evidence is sufficient to support a causal association between fexinidazole and irreversible hepatotoxicity/acute liver failure in patients with CS and adjudicated as an important potential risk. The EU Fexinidazole Summary of Product Characteristics (SmPC) has been amended in section 4.4 to include “risk of severe irreversible hepatotoxicity in patient with Cockayne syndrome” in the section “Special warnings and precautions for the use” of SmPC and corresponding section in the patient information leaflet.
- Fexinidazole has shown cross-resistance in in vitro and in vivo studies, suggesting a common mode of resistance and action amongst nitro drugs based on the MoA of parasite killing. Whilst it is unlikely, the potential for the development of resistance to fexinidazole or to NECT (used as rescue treatment) in HAT patients failing to respond to fexinidazole cannot be fully discounted. Development of resistance to fexinidazole, cross resistance between fexinidazole and nifurtimox is already considered as important potential risk for *T.b. gambiense* HAT indication. Based on the possibilities of resistance Development of resistance to fexinidazole is also considered as important potential risk for *T.b. rhodesiense* HAT indication.

The following reclassification is proposed in RMP v3.1:

- As per Type II variation assessment report dated 14 September 2023 on EU-RMP version 3.0 (submitted by Sanofi under procedure EMEA/H/W/002320/II/0016), the EMA recommended to reclassify important potential risk of "Vomiting" to important identified risk considering vomiting is a known adverse reaction of fexinidazole. Moreover, vomiting is a very frequent ADR of fexinidazole (see current EU-SmPC dated December 2022) and is a nitroimidazole class-effect (fexinidazole monography in Martindale applies to that of metronidazole).

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for fexinidazole:

- Important identified risks:
  - Psychiatric events[1]
  - Vomiting
- Important potential risks:
  - Pro-arrhythmic effect
  - Severe infection secondary to drug-induced neutropenia
  - Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)
  - Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[2]
  - Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)
- Missing information:
  - Use in pregnancy/lactation
  - Use in children <6 years old or less than 20 kg

[1] Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

[2] Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

SVII.3.1 Presentation of important identified risks and important potential risks

Table 27 - Identified risk: Psychiatric events

Identified Risk	**Psychiatric events**[a]
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Nitroimidazole class effect HAT studies Chagas study
Characterization of the risk	During the HAT Studies TEAEs from the Psychiatric disorders SOC in the ITT population were reported in 32% of patients treated with fexinidazole and included mainly insomnia AEs (23%), the majority of which were considered related to treatment. The next most frequently occurring psychiatric AEs occurred far less frequently eg, psychotic disorder (2%), hallucination (3%), agitation (3%) and logorrhoea (2%). Depression only occurred in 4 fexinidazole HAT patients, all in the pivotal study which compared effects of NECT and for which no cases of depression have been reported. In comparison to NECT, in adults and older adolescents with late stage 2 disease, fexinidazole was associated with a greater incidence of psychiatric disorders (18% versus 39%, respectively). In the FEX009 (g-HAT) study, A total of 46 TEAEs pertaining to the SOC psychiatric disorders were reported in 32 out of 174 (18,4%) patients with HAT exposed to fexinidazole; “insomnia” (10.9%) and “anxiety” (6.9%) were the most frequently reported psychiatric events and were assessed as drug-related in most of the cases. In 3 cases in 3 (0.6%) patients were considered as serious: “anxiety” (assessed as related to fexinidazole by both the investigator and sponsor), “confusional state”, and “psychotic disorder due to a general medical condition”. No TEAEs of psychiatric disorders were reported in patients with r-HAT treated with fexinidazole during the FEX007 study. In the FEX004 pivotal study (g-HAT), two patients treated with fexinidazole reported suicidal ideation (one of them with confounding factors), Of the psychiatric events occurring in fexinidazole administered HAT patients, 5 were considered by investigators and/or the sponsor to be serious; 2 cases of personality change and one case each of acute psychosis, psychotic disorder and suicidal ideation; 4 of these events occurred in study DNDiFEX004. No SAE in the psychotic SOC occurred in patients treated with NECT. The 5 psychiatric SAEs were considered resolved. Chagas Studies: In the Chagas study (DNDi-CH-FEXI-001) one patient experienced severe depression leading to suicide attempt and completed suicide. In the FEX012 study, serious adverse event of Depression (Recovered with sequelae) and anxiety (Not recovered) reported from the same patient and both SAEs were assessed as related. However, a literature review by Steel Z et al. (16) indicated that on average, about 29.2% people experienced a common mental disorder across their lifetime. Countries in North and South-East Asia in particular had lower prevalence estimates than other regions of the world. Across both high income and low and middle-income countries, females were more likely to experience a mood or anxiety disorder. The pooled lifetime prevalence was 9.6% for mood disorders and 12.9% for anxiety disorders, respectively. Findings in another review by Erskine HE et al. (17) showed that among the children and adolescents aged 5-17 years old, the global prevalence for mental disorders was 6.7%, with a prevalence of 6.2% for depression and 3.2% for anxiety. A report from the Center for Disease Control and Prevention, Program Performance and Evaluation Office, 2013 (18) revealed that the incidence rate of major depressive episodes in US is 6.7% per year, with a significantly greater lifetime prevalence for major depression among women (11.7%) than men (5.6%).

Identified Risk	Psychiatric events[a]
	This report also indicated that the lifetime prevalence of depression was 6.52%, 4.57%, and 5.17% among whites, blacks, and Hispanics, respectively. Apart from this, the estimated lifetime prevalence of any anxiety disorder is over 15%. In a meta-analysis, Polanczyk GV et al. (19) suggested that the pooled prevalence for any mental disorder was 13.4%. The prevalence of any anxiety disorder, any depressive disorder, attention-deficit disorder, and any disruptive disorder was 6.5%, 2.6%, and 5.7%, respectively. De Souza Lopes C et al. (20) reviewed that insomnia is quite prevalent in general population, with approximately 10-15% suffering from it regularly, and about 25-35% presenting transient or occasional insomnia. The estimates of insomnia prevalence ranged from 10-40%. The prevalence of insomnia symptoms may be estimated at 30% and specific insomnia disorders at 5-10%. Risk factors most commonly associated to insomnia included female gender, age, marital status, income, educational level, and race/ethnicity. In addition, De Souza Lopes C et al. (20) reviewed that insomnia is quite prevalent in general population, with approximately 10-15% suffering from it regularly, and about 25-35% presenting transient or occasional insomnia. The estimates of insomnia prevalence ranged from 10-40%. The prevalence of insomnia symptoms may be estimated at 30% and specific insomnia disorders at 5-10%. Risk factors most commonly associated to insomnia included female gender, age, marital status, income, educational level, and race/ethnicity.
Risk factors and risk groups	Increased risk of serious psychiatric events in patients with psychiatric disorders (history or acute).
Preventability	Routine and additional minimization measures (see [RMP Part V]): Caution should be exercised when using fexinidazole to treat HAT in patients with psychiatric disorders (history or acute), and it is recommended that these patients be hospitalized during the 10 day treatment period.
Impact on the benefit-risk balance of the product	A serious psychiatric event can be life-threatening and result in death.
Public health impact	No public health impact is expected.

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

AE: Adverse Event; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; ITT: Intent-To-Treat; NECT: Nifurtimox-Eflornithine Combination Therapy; r-HAT: *Rhodesiense* Human African Trypanosomiasis; RMP: Risk Management Plan; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event; US: United States.

Table 28 - Identified risk: Vomiting

Identified Risk	Vomiting
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Nitroimidazole class effect HAT studies Chagas study
Characterization of the risk	Data from the pooled analysis of gHAT Studies DNDiFEX004, DNDiFEX005 and DNDiFEX006 showed that gastrointestinal disorders were the most commonly reported TEAEs (vomiting [42%], nausea [35%] and dyspepsia [14%]). There was a trend to increased incidence of vomiting during the loading phase. Treatment was re administered in all patients who vomited within the 60 minute period after administration. In most fexinidazole patients, re-treatment after vomiting was only administered once.

Identified Risk	Vomiting
	In DNDiFEX009 (g-HAT) study prevalence of TEAEs in the other SOCs was similar between inpatients and outpatients: Gastrointestinal disorders SOC (39.0% versus 34.2%), vomiting was reported in 23.6% of the patients (41 out of 174 patients), all non-serious TEAEs of mild to moderate intensity; vomiting was assessed as drug-related in majority of the cases. 6.3% of patients were re-administered once due to vomiting. Nausea reported in 15.5% patient (all non-serious TEAEs). In patients more frequently had TEAEs of vomiting (25.7%, versus 15.8% of outpatients) In FEX007 (r-HAT) study the most frequently reported TEAEs were vomiting. Vomiting was reported in 6/45 patients (13.3%), which represents 30% less than the pooled incidence in previous fexinidazole studies (42%). In the paediatric Study, DNDiFEX006, the incidence of vomiting was higher than seen in the adult studies. There are reports from investigators which suggest that some children may have had problems swallowing the fexinidazole tablets causing them to vomit. During the 10 days of treatment incidence was highest on Day 2 of the loading phase (1200 mg or 1800 mg) (36.0%) and decreased over time during the maintenance phase (600 mg or 1200 mg), ranging from 11.2% (Day 5) to 4.8% (Day 10). No permanent discontinuation of treatment due to vomiting was reported.
Risk factors and risk groups	Increased risk in children.
Preventability	Routine and additional minimization measures (See [RMP Part V]): If a first case of vomiting occurs after receiving Fexinidazole, do not re-dose. Take the next dose the following day using the recommended treatment schedule. If a second event of vomiting occurs after administration of any other dose of Fexinidazole, the healthcare staff responsible of the treatment should decide how to continue the treatment based on the timing of the vomiting after administration and the occurrence of the event within the scheduled dosing regimen
Impact on the benefit-risk balance of the product	Vomiting may be severe and impact completed treatment cure.
Public health impact	No public health impact is expected.

g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Table 29 - Potential risk: Pro-arrhythmic effect

Potential Risk	Pro-arrhythmic effect
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Non-clinical hERG data: fexinidazole M2 induced significant inhibition. Clinical data
Characterization of the risk	In a prospective cohort study of 60 patients (>15 years old) with late-stage HAT and 60 age and gender matched healthy controls in Bandundu, Blum JA et al (2007) (21) reported that major ECG alterations were significantly more frequent in HAT patients than in healthy controls (71% versus 18%). Symptoms consistent with heart failure such as exertional dyspnea (19% versus 1.7%) or palpitations (18% versus 5%) occurred more frequently in HAT patients than in controls. The median NT-proBNP was significantly higher in HAT patients than in controls (85.2 versus 28 pg/ml). (22) conducted an analysis of ECG findings among a total of 523 patients including 406 patients with first stage HAT were recruited in the Democratic

Potential Risk	Pro-arrhythmic effect
	Republic of Congo, Angola and Sudan between 2002 and 2007 in a series of clinical trials, 61 healthy volunteers and 56 patients with second stage HAT. In this analysis, patients with HAT had significantly more frequent prolonged QTc interval than healthy controls, with 0% in healthy subjects, 11.1% in patients with first stage HAT, and 12.5% in those with second stage HAT. More frequent repolarization changes were also observed in patients with HAT than healthy subjects (ie, 6.6% in healthy subjects, 35.2% in patients with first stage HAT and 32.1% in those with second stage HAT). In both healthy subjects and patients, administration of fexinidazole resulted in an increase in QTcF of about 20 ms. The concentration-response analyses indicated that this increase in QTcF is most likely caused by metabolite fexinidazole sulfone (M2) and not by fexinidazole or metabolite M1, which is consistent with results obtained in the in vitro hERG study. For fexinidazole sulfone M2, an Emax model provided the best fit. This model predicts at the geometric mean maximum concentration of the therapeutic regimen a maximum increase (90% confidence interval) from baseline in QTcF of 18.0 ms (90% CI 16.4; 19.6) and 14.9 ms (90% CI 12.8; 17.1) in adult and pediatric patients suffering from HAT. Both in healthy subjects and in most patient populations, administration of fexinidazole resulted in an increase in heart rate of about 10 bpm. No consistent effects on PR and QRS intervals were observed. Two occurrences of QTc values greater than 500 ms were documented during the pivotal study (DNDiFEX004) in HAT patients about 10 days after last fexinidazole administration, ie, when M2 concentrations are expected to be near baseline levels. There were no TEAEs suggesting a life-threatening ventricular arrhythmia reported. The other relevant ECG finding observed in the clinical studies thus far performed with fexinidazole is the chronotropic effect both in healthy volunteers and in patients, administration of fexinidazole resulted in an increase in HR of about 10 bpm related to the TEAE of palpitations. However, QTcF increases were rarely observed in patients with increased HR. In DNDIFEX009 (g-HAT) study ECG safety report: treatment with fexinidazole caused an increase from baseline in the QTcF interval of about 10 ms with a maximum increase reported at D4. The upper limit of the 90% CI exceeded the regulatory threshold of 10 ms. The magnitude of the observed QTcF increase after dosing is consistent with that reported after fexinidazole treatment during the studies performed in adults DNDiFEX004 study) and children (DNDiFEX006). Two cardiac disorders were reported including: 1 TEAE of myocardial ischaemia at D11 (CTCAE grade 1, not related by investigator) and 1 TEAE of palpitations at D4 (CTCAE grade 1, related by investigator). In DNDiFEX007 (r-HAT) study, heart rate was very frequently elevated (abnormal non-clinically significant) at baseline, with 75% of patients with ≥98 bpm, gradually decreasing from baseline to EoH, with a mean (SD) ranging from 106.2 bpm (16.4) at baseline to 87.2 bpm (11.6) at EoH. In DNDiFEX007 (r-HAT) study a total of 8 patients (17.8%) had non-serious ECG abnormalities reported as TEAEs: electrocardiogram U-wave abnormality (4 events in 3 patients), electrocardiogram QT prolonged (2 patients), electrocardiogram T-wave abnormality (1 patient), electrocardiogram T-wave inversion (1 patient), and sinus tachycardia (1 patient). The 2 events of electrocardiogram QT prolonged and 2 events of electrocardiogram U-wave abnormality were considered related to study treatment in 3 patients (6.7%). All events were mild to moderate in intensity and resolved within 7 to 65 days (except sinus tachycardia in one patient which was severe in intensity and had not resolved until the patient's death). In Chagas study (DNDi FEX012) no relevant changes from baseline to post-baseline visits, no apparent trends over time, and no notable differences between the 3 FEXI dose groups in ECG values over time were observed. For the majoritiy of patients (at least 69.8% per visit) the ECG values were assessed as normal. For the ECGs that were assessed as abnormal, the majority were assessed as NCS. One TEAE of cardiac disorder was reported Defect conduction

Potential Risk	Pro-arrhythmic effect
	intraventricular (moderate) at a dose of 6.0 g. At baseline ECG values on Day 1 were assessed as abnormal clinically significant. On Day 22, abnormal NCS ECG results were reported and TEAE resolved. The investigator assessed the TEAE as related to fexinidazole. *During the development program of fexinidazole, there was no sudden death, syncope, dizziness or documented ventricular arrhythmias. One HAT patient experienced an event of tachycardia: all the ECGs for this patient were analyzed as normal by the cardiologist with a nonclinical relevant sinusal tachycardia***.** Therefore, the clinical safety of the fexinidazole development program was reassuring regarding the lack of clinical symptoms suggesting the occurrence of a TdP although the total number of treated subjects is still small. Based on the Emax model, and on the fact that the probability of observing a TdP after a QTc prolongation is generally very low for drugs known to prolong the QTc (23) and considering the low number of patients that will receive fexinidazole (~1000/year), it is not justified to perform an ECG before, during or after fexinidazole administration.
Risk factors and risk groups	Patients with known congenital prolongation of QTc interval, uncorrected electrolyte abnormalities (eg, hypokalemia or hypomagnesemia), history of symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure or family history of sudden death. Concomitant use of medicinal products that prolong QT interval, induce bradycardia or hypokalaemia: • Anti-arrhythmics class IA (eg, quinidine, hydroquinidine, disopyramide) • Anti-arrhythmics class III (eg, amiodarone, sotalol, dofetilide, ibutilide) • Tricyclic-antidepressive agents (eg, imipramine, amitriptyline) • certain antimicrobial including some antituberculosis agents (saquinavir, atazanavir, erythromycin IV, parfloxacin, moxifloxacin, ofloxacin, levofloxacin, clofazimine, delamanid, pentamidine, certain antimalarials particularly halofantrine) • certain antihistaminics (terfenadine, astemizole, mizolastine) • others (cisapride, vincamine IV, iphemanil, lithium). • Antipsychotics could be used if required, in hospitalized patients under close monitoring.
Preventability	Routine and additional minimization measures (See [RMP Part V])**:** Caution should be exercised in patients at risk as defined above. If patients are, or need to be, treated with drugs known to prolong QTcF interval or to induce bradycardia, either do not initiate fexinidazole until such drugs are eliminated from the body (allow a washout period of 5 half-lives), or do not start such drugs until fexinidazole is eliminated from the body (allow a washout period of 7 days).
Impact on the benefit-risk balance of the product	Cardiovascular events may be life threatening or result in death.
Public health impact	No public health impact is expected.

BPM: Beats Per Minute CS: Clinically Significant; EoH: End of Hospitalization; ECG: Electrocardiogram; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; HR: Heart Rate; IV: Intravenous; NCS: Non-Clinical Significant; TdP: Torsades de pointes; hERG: human Ether-a-go-go-Related Gene; QTcf: corrected QT interval by Fridericia; r-HAT: *Rhodesiense* Human African Trypanosomiasis; SD: Standard Deviation; TEAE: Treatment Emergent Adverse Event.

Table 30 - Potential risk: Severe Infection secondary to drug-induced neutropenia

Potential Risk	Severe infection secondary to drug-induced neutropenia
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Decrease in neutrophil count observed in a few patients in the clinical studies.
Characterization of the risk	In HAT indication, fexinidazole induced mild decrease in absolute neutrophil count (approximately 500 per μL). Onset during 10 days. Twelve of 619 patients (2%) exposed to fexinidazole in the pooled population of the 3 HAT studies experienced TEAEs of neutropenia, with no apparent difference in frequency based on HAT stage. Of these, 4 experienced non-serious TEAEs of neutropenia that were considered by the Investigator as possibly related to fexinidazole (1 patient in Study DNDiFEX005 and 3 patients in Study DNDiFEX006), 1 of which was also severe in intensity but none was associated with any infectious complications. Analysis of patients with infection also showed no association with neutropenia. In DNDiFEX009 (g-HAT) and DNDiFEX007 (r-HAT) studies no TEAEs of neutropenia were reported. In the study conducted in Chagas Bolivian patients a dose-related neutropenic effect of fexinidazole was detected. Patients were administered a different dose regimen of fexinidazole from that administered to HAT. Eight of the 40 patients (20%) experienced symptomatic and reversible within one-week SAEs of severe neutropenia (Grade 3-4) (NCI CTCAE). The cases of neutropenia were not associated with increased risk of infections and occurred quite late during treatment with a nadir of approximately 9 weeks. In DNDi FEX012 (Chagas study) 1 patient presented with 2 occurrences of non-serious grade 2 (moderate) TEAE of leukopenia (at D1 and D7 of treatment period, recovered after 14 days) that were assessed as not related by the investigator. No hematological abnormalities were identified in this study. Pharmacokinetic/Pharmacodynamic analysis supports difference between HAT and Chagas. Fexinidazole does not show a significant risk of neutropenia in HAT patients. Prevalence/incidence in general African or sub-Saharan African population In a US inner city, multiethnic outpatient population of older subjects ≥65 years, the prevalence of neutropenia defined using a cutoff of 1500 neutrophils per microliter was 2.9% in African Americans. (24) A population-based cross sectional study of National Health and Nutrition Examination Survey participants during years 1999 to 2004, the prevalence of neutropenia was reported to be 4.47% in African American population. (25) No epidemiological data are available on incidence or prevalence of neutropenia in unexposed target population (ie, untreated patients with HAT). Prevalence/incidence in exposed target population (ie, treated patients with HAT) A total of 48 patients with late-stage *T. b. gambiense* sleeping sickness (31 from a NECS and 17 from, BTT) were treated with a combination of nifurtimox and eflornithine in northwest Uganda. The combined results from both trials reported an incidence of neutropenia of 27.1% (13 out of 48). (26) In a randomized, open-label, active control, phase III, non-inferiority trial performed at 4 HAT treatment centres in the Republic of the Congo, patients with confirmed second-stage *T. b. gambiense* infection were randomly assigned to receive intravenous eflornithine (400 mg/kg/d, every 6 h; n = 144) for 14 days or intravenous eflornithine (400 mg/kg per day, every 12 h) for 7 days with oral nifurtimox (15 mg/kg/d, every 8 h) for 10 days (NECT; n = 143). The incidence of neutropenia was reported to be 33.1% and 15.5% in eflornithine and NECT groups, respectively. (27) In a randomized, open-label, active-control, phase III clinical trial conducted at the sleeping sickness treatment centre, Republic of Congo, patients with second stage HAT were randomly assigned to receive eflornithine alone (400 mg/kg/d given intravenously every 6 h for 14 days) or eflornithine (400 mg/kg/d given intravenously every 12 h for 7 days) plus nifurtimox (15 mg/kg/d

Potential Risk	Severe infection secondary to drug-induced neutropenia
	given orally every 8 h for 10 days). The incidence of neutropenia was 56.9% and 21.2% in eflornithine alone (n = 51) and eflornithine plus nifurtimox groups (n = 52), respectively. (10) In a randomized, open-label, active control, parallel clinical trial conducted at the sleeping sickness treatment centre in Uganda, 53 patients with late-stage g-HAT were randomly assigned to receive melarsoprol-nifurtimox (n = 18), melarsoprol-eflornithine (n = 18), and nifurtimox-eflornithine (n = 17). One (1) patient from melarsoprol-eflornithine group and 3 patients from nifurtimox-eflornithine group developed major neutropenia. (28)
Risk factors and risk groups	Human African Trypanosomiasis patients with evidence, or history, of blood dyscrasia.
Preventability	Routine and additional minimization measures (See [RMP Part V]): Fexinidazole should be used with caution in patients with evidence, or history, of blood dyscrasia. Although no case of severe infection was reported, patients treated with fexinidazole will be advised to return to the clinic in case of fever or clinical signs of suspected infection.
Impact on the benefit-risk balance of the product	Severe infection which can range from severe to life-threatening and may lead to death.
Public health impact	No public health impact is expected.

BTT: Bitherapy Trial; CTCAE: Common Terminology Criteria for Adverse Event; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; NCI: National Cancer Institute; NECS: Nifurtimox-Eflornithine Case Series, NECT: Nifurtimox-Eflornithine Combination Therapy; PK/PD: Pharmacokinetics/Pharmacodynamics; r-HAT: *Rhodesiense* Human African Trypanosomiasis; SAE: Serious Adverse Event; TEAE: Treatment Emergent Adverse Event; US: United States.

Table 31 - Potential risk: Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)

Potential Risk	Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)
Potential mechanism	Unknown. Potential adaptive immune mechanism in Chagas patients.
Evidence source(s) and strength of evidence	Increase in transaminase observed in some patients treated with fexinidazole in the Chagas study: Evidence effect of cumulative metabolite M2 exposure.
Characterization of the risk	In the Phase I Study DNDiFEX001, there was one case of ALT increase up to 30 x ULN in a patient who received a high dose of 3600 mg for 14 days with mild clinical symptoms and rapid resolution. Liver tests in HAT clinical trials (DNDiFEX004 - DNDiFEX005 - DNDiFEX006) did not show significant liver injuries. Indeed, abnormalities are limited to mild asymptomatic increase of liver enzymes below definition of acute liver injury. And no clinically significant increase in transaminase has been reported although transaminase increase is considered an alert sign. There is no case of significant liver injury or case with Hy's law criteria. There is no case with delayed or protracted course. Generally, any increases seen in liver function tests between baseline and EoT in the HAT studies were mild, transient and reversible In the pooled analysis, changes in ALP, ALT, AST and bilirubin over time did not cause mean levels to stay outside of the normal reference ranges. In DNDiFEX009 (g-HAT) study no TEAE related to abnormal liver lab test results or liver injuries were reported.

Potential Risk	Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)
	In DNDiFEX007 (r-HAT) study no hepatic event reported in the hepatic disorders or investigations SOCs. In Chagas study: 40% patients reported chronic or acute increase in ALT or AST >3 x ULN (versus none in the placebo arm). In these patients liver tests returned to normal including the 8 cases with delayed or protracted course. So that, there is no sign of severity. These observations were reversible and no Hy's law cases were reported. In DNDi FEX012 (Chagas study) 2 TEAEs of ALT increased and AST increased were reported in one patient in the FEXI 6.0 g group (mild intensity, start at Day 22, resolved after 56 days; assessed by the investigator and sponsor as not treatment-related). No liver injuries were identified in this study. The profile of abnormalities of liver tests with fexinidazole is different between HAT and Chagas disease: In HAT, liver test abnormalities are less frequent, with lower values and without prolonged course. Chagas disease may be a predisposing condition with a potential for autoimmunity. Pharmacokinetic/Pharmacodynamic analysis supports difference between HAT and Chagas with lower risk of liver toxicity in HAT patients. Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, another nitroimidazole agent structurally related to fexinidazole, have been reported in patients with Cockayne syndrome.
Risk factors and risk groups	Patients with clinical signs of cirrhosis or jaundice. Patients with CS.
Preventability	Routine and additional minimization measures (See [RMP Part V]) Fexinidazole is contraindicated in patients with clinical signs of cirrhosis or jaundice. SmPC and Patient Information Leaflet Warning about hepatic impairment and Cockayne syndrome In patients with Cockayne syndrome, fexinidazole should therefore be used only if no adequate alternative treatment is available. Patients treated with fexinidazole and suffering from Cockayne syndrome should be hospitalized in order to allow close monitoring and stop treatment if necessary. No HAT and/or Chagas patients with Cockayne Syndrome included in clinical studies.
Impact on the benefit-risk balance of the product	Effects on liver can range from clinically insignificant to fulminant hepatic failure resulting in death.
Public health impact	No public health impact is expected.

ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CS: Cockayne Syndrome; EoT: End of Treatment; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; PD: Pharmacodynamics; PK: Pharmacokinetic; r-HAT: *Rhodesiense* Human African Trypanosomiasis; SOC: System Organ Class; SmPC: Summary of Product Characteristics; ULN: Upper Limit of Normal.

Table 32 - Potential risk: Drug-drug interaction (DDI) with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19

Potential Risk	Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[a]
Potential mechanism	Fexinidazole and its metabolites have the potential to inhibit CYP1A2, CYP2C19 and CYP3A4 in vitro. (Sanofi ICH0106 study). An in vivo clinical DDI study (INT15307) has shown that repeated administration of fexinidazole using the therapeutic loading dose regimen increased

Potential Risk	Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[a]
	by around 2-fold the exposure of caffeine (CYP1A2 probe) and omeprazole (CYP2C19 probe). It is predicted that, in vivo, fexinidazole could increase the exposure of medicinal products highly metabolized by CYP3A4 and with a significant CYP3A4 first pass, such as lovastatin, simvastatin or nisoldipine. Potential interaction: Fexinidazole could potentially increase the exposures of drugs metabolized mainly by CYP1A2 (such as caffeine, duloxetine, melatonin, tacrine, tizanidine, and theophylline),) or CYP2C19 (such as omeprazole, lansoprazole, diazepam, and mephenytoin) or CYP3A4 (such as lovastatin, simvastatin or nisoldipine).
Evidence source(s) and strength of evidence	Sanofi ICH0106 study INT15307
Characterization of the risk	Risk of increased exposure of concomitant drugs taken by patients mainly metabolized by CYP1A2 (such as caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline) or CYP2C19 (such as omeprazole, diazepam, mephenytoin), or CYP3A4 (such as lovastatin, simvastatin or nisoldipine) resulting in exaggerated and prolonged main effects and also side effects of these drugs. One additional study, (INT17144 is ongoing to assess in vivo interaction on midazolam (CYP3A4 probe drugs).
Risk factors and risk groups	None
Preventability	Routine and additional minimization measures (See [RMP Part V]). Caution is advised when fexinidazole is concomitantly used with drugs which are metabolized by CYP1A2, CYP2C19 and CYP3A4.
Impact on the benefit-risk balance of the product	Increased risk for adverse reactions associated with increased concentrations of the drug due to inhibition of either CYP1A2, CYP2C19 or CYP3A4 by fexinidazole
Public health impact	No public health impact is expected.

a Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CYP: Cytochrome P450; DDI: Drug-Drug Interaction; TEAE: Treatment Emergent Adverse Event.

Table 33 - Potential risk: Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)

Potential Risk	Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)
Potential mechanism	Nitromidazole class effect. NTRI gene mutation, reducing the NADH availability for its MoA.
Evidence source(s) and strength of evidence	Mutliple researches on nitroimidazole resistance induction in trypanosomes. (29)(30)
Characterization of the risk	In light of the low expected number of cases and that the total parasites burden is low, the potential of this resistance is considered low. Development of cross resistance between fexinidazole and nifurtimox is not applicable for *T.b. rhodesiense* HAT indication.

Potential Risk	**Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)**
Risk factors and risk groups	As for other drug resistance, the risk factors could be related to incomplete treatment, inappropriate use of the compound, and repeated exposure to the treatment. Human African trypanosomiasis patients treated with nitro imidazole compounds or off-label.
Preventability	Routine and additional minimization measures (See [RMP Part V]). Avoidance of inappropriate use. The availability of fexinidazole for trained HCPs in selected HAT health centers and its controlled distribution in these centers should prevent inappropriate use.
Impact on the benefit-risk balance of the product	Parasite or cross resistance may reduce the efficacy in treating HAT.
Public health impact	Fexinidazole-resistance appears unlikely to develop in HAT patients because it is estimated that about one thousand HAT patients will be treated at the time of fexinidazole roll-out. The lowering number of HAT patients greatly reduces the probability of transmission and consequently the probability of fexinidazole repeated exposure. Development of cross resistance between fexinidazole and nifurtimox is not applicable for *T.b. rhodesiense* HAT indication. The public health impact is thus considered low.

HAT: Human African Trypanosomiasis; HCP: Healthcare Professional; MoA: Mechanism of Action; NADH: Nicotinamide Adenine Dinucleotide.

SVII.3.2 Presentation of the missing information

Table 34 - Missing information: Use in pregnancy/lactation

Missing Information	Use in pregnancy/lactation
Evidence source(s) and strength of evidence	In animal studies, effects on embryo-fetal development were observed only at doses harmful to the dams. These effects were considered as secondary to maternal toxicity. Plasma concentrations of Fexinidazole and of its metabolites at these dose levels were low as compared to clinical exposures. Fexinidazole, its M1 and M2 metabolites are excreted in rat milk at the same concentrations than those in the plasma of the lactating mother. Effects on suckling rat pups were limited to transient growth retardation at high dose level only. DNDiFEX009 (g-HAT) and DNDiFEX007 (r-HAT) clinical studies.
Anticipated risk/consequence of the missing information **Or Population in need for further characterization**	Limited data are available in pregnant and lactating women from DNDiFEX009 (g-HAT) and DNDiFEX007 (r-HAT) clinical studies. The newborns whose mothers were exposed to fexinidazole during pregnancy were healthy and developing normally, except for 1 fatal case due to early neonatal infection. The breastfed newborns exposed to fexinidazole were healthy and developing normally except in two fatal cases due to concomitant conditions (anemia complicated by malaria). As a precautionary measure, it is preferable to avoid the use of Fexinidazole during the 1st trimester of pregnancy, and the benefit-risk of treatment with fexinidazole should be evaluated during the 2nd and 3rd trimesters. On the basis of the non-clinical data no detrimental effect of the use of fexinidazole in lactating women is expected in their children. As a precautionary measure the decision to use fexinidazole during breast-feeding should take into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Missing Information	Use in pregnancy/lactation

g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; PK: Pharmacokinetic; r-HAT: *Rhodesiense* Human African Trypanosomiasis.

Table 35 - Missing information: Use in children <6 years old or less than 20 kg

Missing Information	Use in children <6 years old or less than 20 kg
Evidence source(s) and strength of evidence	Children <6 years old or less than 20 kg were not involved in the clinical development of fexinidazole. However, assuming the targeted population of the indication will include children, the use of fexinidazole in these children is considered as missing information.
Anticipated risk/consequence of the missing information **Or Population in need for further characterization**	The absence of clinical data in pediatric population is reflected in the claimed indications for use in children above 6 years old or 20 kg body weight.

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risks	Psychiatric events[a]
	Vomiting
Important potential risks	Pro-arrhythmic effect
	Severe infection secondary to drug-induced neutropenia
	Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)
	Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[b]
	Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)
Missing information	Use in pregnancy/lactation
	Use in children <6 years old or less than 20 kg

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

b Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CS: Cockayne Syndrome; CYP: Cytochrome P450; HAT: Human African Trypanosomiasis.

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of fexinidazole.

A pharmacovigilance plan based on the successful pharmacovigilance experience of the NECT (31) has been set up with the World Health Organization (WHO) and implemented at the time of fexinidazole (for g-HAT and r-HAT) roll out (more details in [RMP Part V]). It includes a system of pharmacovigilance dedicated to fexinidazole treatment as part of NSSCP activity as per WHO interim guidelines 2019. WHO is in charge of fexinidazole distribution and of the implementation of the dedicated pharmacovigilance system.

The safety profile of fexinidazole will continue to be further characterized in real-life setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) relating to adverse events, and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

During New Drug Application (NDA) procedure, as a postmarketing requirement, US Food and Drug Administration (FDA) has requested the applicant (Sanofi/DNDi) to conduct a clinical DDI trial to evaluate the effect of repeat doses of fexinidazole tablets on the pharmacokinetics of midazolam, which is a cytochrome P450 (CYP) 3A4 sensitive drug substrate. The study protocol has been submitted to US FDA in September 2021 and final study report submission to US FDA is scheduled by March 2024.

Table 36 - Additional pharmacovigilance activities (category 3) summary

FEXINC09395 (for g-HAT)
Study short name and title
Post-authorization safety study of Fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Rationale and study objectives
Rationale:
Fexinidazole is a new treatment modality to be prescribed for the treatment of HAT in countries where the local pharmacovigilance system may be poorly organized. As was done for NECT (31) a close pharmacovigilance process will be implemented. Additionally, this will ensure that adequate supervision is maintained for patients taking treatment at home.
In the context of the implementation of the WHOs Pharmacovigilance system, data collection of fexinidazole-treated HAT patients in the NSSCP has been endorsed by PRAC on 26-Jun-2018. The study can be considered as an additional Pharmacovigilance activity and should be included in the pharmacovigilance plan as a category 3 PASS.
Study objectives:
The primary objective of this PASS is to assess the safety of fexinidazole in field conditions of use.

The secondary objective to assess effectiveness of fexinidazole, in real life use by evaluating occurrence of relapse at 12 and 24 months of follow-up.

Study design

The PASS is based on the analysis of the data prospectively collected by the NSSCP/WHO PHP in selected sub-Saharan African countries as per WHO guidelines adopted by NSSCP.

Study populations

Patients identified with sleeping sickness and treated with fexinidazole.

Milestones

Milestone	Planned date
Database delivery by WHO	Q1 2025
Start of data analysis	Q2 2025
Final report of study results	Q1 2026

WHO: World Health Organization; Q: Quarter.

No specific interim reports are planned but standard reporting based on PBRERs will be issued.

AUC: Area Under Curve; CYP: Cytochrome P450; DDI: Drug-Drug Interaction; EMA: European Medicines Agency; FDA: Food and Drug Administration; g-HAT: *Gambiense* Human African trypanosomiasis; NECT: Nifurtimox-Eflornithine Combination Therapy; NSSCP: National Sleeping Sickness Control Program; PASS: Post-Authorization Safety Study; PBRER: Periodic Benefit-Risk Evaluation Report; PHP: Public Health Program; Q: Quarter; WHO: World Health Organization.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 37 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019 Planned Category 3	The primary objective of this PASS will be to assess the safety of fexinidazole in field conditions of use. The secondary objective will be to describe the effectiveness of fexinidazole, in real life use by evaluating occurrence of relapse at 12 and 24 months of follow-up.	Presence of any adverse side effects related to fexinidazole: Any case of sudden death during treatment Delivery outcomes in women exposed to fexinidazole during pregnancy Two-year follow-up after delivery among children who received	Database delivery by WHO Start of data analysis Final report of study results.	Q1 2025 Q2 2025 Q1 2026 No specific interim reports are planned but standard

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		in utero exposure to fexinidazole.		reporting based on PBRERs will be issued.

CYP: Cytochrome P450; FSI: First Subject In; g-HAT: *Gambiense* Human African trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; PASS: Post-Authorization Safety Study; PBRER: Periodic Benefit-Risk Evaluation Report; Q: Quarter; WHO: World Health Organization.

RISK MANAGEMENT PLAN - PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for fexinidazole.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

The routine risk minimization measures include specific safety information into the labeling documents (both SmPC and Package Leaflet [PL]) and a specific packaging with visual instructions for use (see [Annex 6]). These instructions provide information/guidance on how to take fexinidazole to ensure compliance to the treatment and avoid medication errors. The specific packaging contains the exact number of tablets for the total duration of the treatment period. Of note different packaging are available for adults and children, as the posology is different (mock-up of the packaging located in the [CTD M1.3.2 Mock-up]).

Table 38 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Psychiatric events[a]	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in section 4.4 Special warnings and precautions for use; section 4.7 Effects on ability to drive and use machines and section 4.8 Undesirable effects. • PL: Labeled in section 2 What you need to know before you take FEXINIDAZOLE WINTHROP - Warnings and precautions and section 4 Possible side effects. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Vomiting	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in section 4.2 Posology and method of administration and section 4.8 Undesirable effects. • PL: Labeled in section 3 How to take FEXINIDAZOLE WINTHROP - If you vomit after taking FEXINIDAZOLE WINTHROP and section 4 Possible side effects. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Pro-arrhythmic effect	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use; section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects.

Safety concern	Routine risk minimization activities
	• PL: Labeled in section 2 What you need to know before you take FEXINIDAZOLE WINTHROP - Warnings and precautions and other medicines FEXINIDAZOLE WINTHROP; Section 4 Possible side effects. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Severe infection secondary to drug-induced neutropenia	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects. • PL: Labeled in section 2 What you need to know before you take FEXINIDAZOLE WINTHROP - Warnings and precautions and section 4 Possible side effects. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in section 4.3 Contraindications; section 4.4 Special warnings and precautions for use; and section 5.1 Pharmacodynamic properties. • PL: Labeled in section 2 - What you need to know before you take Fexinidazole; section 4 Possible side effects. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[b]	**Routine risk communication:** • SmPC: Labeled in section 4.5 Interaction with other medicinal products and other forms of interaction; and section 5.2 Pharmacokinetic properties. • PL: Labeled in section 2 - What you need to know before you take Fexinidazole Other medicines and FEXINIDAZOLE WINTHROP. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Development of resistance to fexinidazole (For *T. b. gambiense* and *T. b. rhodesiense* HAT indications), cross	**Routine risk communication:** SmPC: Labeled in section 5.1 Pharmacodynamic properties.

Safety concern	Routine risk minimization activities
resistance between fexinidazole and nifurtimox (For *T. b. gambiense* HAT indication only)	**Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Use in pregnancy/lactation	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in sections 4.6 Fertility, pregnancy and lactation; and section 5.3 Preclinical safety data. • PL: Labeled in section 2 - What you need to know before you take FEXINIDAZOLE WINTHROP - Pregnancy, breast-feeding, and fertility. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Use in children <6 years old or less than 20 kg	**Routine risk communication:** • Information related to this risk is reported into the SmPC and the PL. • SmPC: Labeled in sections 4.1 Therapeutic indications; and 4.2 Posology and method of administration, • PL: Labeled in section 2 What you need to know before you take FEXINIDAZOLE WINTHROP - Use in children. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

b Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline) CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CS: Cockayne Syndrome; CYP: Cytochrome P450; HAT: Human African Trypanosomiasis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

The additional risk minimization measures consist in a comprehensive program, including a controlled access program, controlled distribution and educational program.

The controlled access program is organized for minimizing the significant public health and individual patient impact of sleeping sickness in endemic countries. Fexinidazole would not otherwise be available without such a program as patient access is contingent on fulfilling specific requirements that will be defined by NSSCP in collaboration with WHO prior to being prescribed.

Given the severity of the HAT disease, the endemic sub-Saharan countries currently organize the optimal care of HAT patients from particularly remote rural areas only in specific healthcare centers identified and supervised by the NSSCPs. In these centers, patients are treated by the currently available HAT treatments, and their safety is supervised by healthcare professionals (HCPs) educated to the treatment of HAT.

In line with the current management of HAT in endemic countries and to secure an appropriate and safe supervision of patients with this new treatment, the use of fexinidazole is restricted in the identified healthcare centers. In these centers the healthcare staff should be trained to dispense and follow-up fexinidazole treatment to HAT patients in line with the prescribing conditions described in the updated WHO HAT treatment guidelines (Version May 2019). (32)

Conjointly with this program, a controlled distribution system has been set up to ensure that distribution fexinidazole is restricted to selected healthcare facilities, and its use reserved to HCPs trained by the NSCCPs in collaboration with WHO.

Fexinidazole is distributed following the same procedure in place for the distribution of current HAT treatments NECT, pentamidine, melarsoprol, suramin), ie, through the WHO neglected tropical diseases department to NSSCPs and from there to the treatment centers.

In more details, the centers treating HAT patients (g-HAT and r-HAT) report the number of diagnosed cases and their need for products to the NSSCP for national consolidation; this data is then transferred to the WHO local office. Each national WHO office reports the data to the WHO headquarters (Geneva), where final consolidation takes place based on the number of cases reported and subsequent treatment needs. The WHO Geneva then holds regular forecasting meetings with drug manufacturers (Sanofi and Bayer) for initiating manufacturing of the requested batches to finally supply the finished products to Medecins Sans Frontieres/Doctors Without Borders (MSF) Logistiques at Bordeaux, France. Under control and supervision by WHO Geneva, MSF ships the products to each country, where the WHO local office receives the shipment and takes care of clearing customs. Once in the country, NSSCP takes over and distributes the products to each of the treating centers, based on their previously declared needs. Products are stored at each center and are only used under HCP supervision and for treating patients.

Educational materials include simplified and visual HCP and patient guide with visual instructions to facilitate the understanding of the instructions and recommendations (see [Annex 6]). The guides (in [Annex 6]) are the ones used in the clinical study FEX09 and in the health centers. Of note, these guides should be developed by WHO in collaboration with the NSSCPs.

The additional measures controlled access program/controlled distribution ensure a safe use of fexinidazole but are not linked to a specific safety concern, as they apply to all.

Table 39 - Additional risk minimization measures

Controlled access program	
Objectives	Fexinidazole will only be prescribed and available in specialized health facilities selected by the NSSCPs to ensure having HCPs knowledgeable on the correct use, supervision and follow-up of fexinidazole administration in HAT patients (g-HAT and r-HAT) according to recommendations and guidance from the NSSCPs in collaboration with WHO. These centers will have the obligation to declare the case(s) of sleeping sickness: this is conditioning the fexinidazole supply to the health centers by NSSCPs. Fexinidazole will not otherwise be available without the controlled access program where patient access is contingent on fulfilling specific requirements defined by the NSSCPs.
Rationale for the additional risk minimization activity	In endemic countries the controlled access program supervised by the NSSCP in collaboration with WHO is the sole organization managing the treatment of HAT (g-HAT and r-HAT). There is no other possibility to treat HAT patients (g-HAT and r-HAT) out of the health centers selected by the NSSCP. Therefore, as a new HAT treatment (for g-HAT and r-HAT) fexinidazole will automatically be managed by the NSSCP.
Target audience and planned distribution path	Health care professionals working in selected Health centers as defined by the NSSCPs.
Plans to evaluate the effectiveness of the interventions and criteria for success	Fexinidazole will not be available without a controlled access program. Once Ministries of Health of endemic countries have included fexinidazole in the national treatment guidelines, they will identify sites where fexinidazole will be used. The countries will communicate to WHO on the training needs and identify the staff and the list of the centers to be trained. Training of trainers will be organized and coordinated by the WHO. The trained staff will in turn train the HCPs of the identified centers to ensure having HCPs knowledgeable on the correct use, supervision and follow-up of fexinidazole administration. Other effectiveness of this risk minimization measure will be assessed by routine (for g-HAT and r-HAT) and additional pharmacovigilance practices (for g-HAT). The pharmacovigilance activities will be conducted in collaboration with WHO. Pharmacovigilance cases will be forwarded to Sanofi Pharmacovigilance by WHO. A pharmacovigilance plan based on the successful pharmacovigilance experience of the NECT (31) has been agreed with the WHO for implementation at the time of fexinidazole roll out (for g-HAT and r-HAT): As reported by Franco et al (2012):" *In 2010, an active pharmacovigilance system for assessing the safety and efficacy of NECT in routine use was set up through WHO. The system was based on the collection and analysis of NECT safety and efficacy in regular use in different settings. Safety is assessed from characterization of s AE during treatment, and efficacy assessed from the register of relapses in patients during the 2 years following treatment.* *For the pharmacovigilance of safety, simplified forms were developed by expert consensus and validated with a group of the users.* *The forms were filled for each patient presenting any adverse event during the treatment with NECT by the professional in charge of the patient (medical officer, clinical officer, or nurse) and sent quarterly straight to WHO or through the NSSCP".* *Training in pharmacovigilance and the use of the report forms was included during the guidance sessions for staff of disease endemic countries in the use of the NECT kit. The report forms were provided to the centers implementing NECT.*

	The qualifications of health staff in charge of HAT case management, the limited resources, the isolation, and difficulties in communication of the centers treating the cases were considered as well as the attempt to avoid overload of work. *As required by regulation in pharmacovigilance, these data have been communicated to the manufacturers.* *This simplified pharmacovigilance system has provided key information in the routine use of the NECT protocol for gambiense trypanosomiasis. In spite of the isolation and limited resources in most of the treatment centers, awareness of the importance and usefulness of the system has given a satisfactory reporting rate.*
Controlled distribution	
Objectives	To make sure fexinidazole will only be distributed to and available in specialized health centers identified by the NSSCPs. This measure will ensure all the steps of the chain distribution are controlled and tracked by the NSSCPs up to the specialized health center.
Rationale for the additional risk minimization activity	For the same reasons than for the controlled access program, and in line with the need for an effective supervision of HAT (g-HAT and r-HAT) treatment by the NSSCPs, the drug product will only be distributed in the dedicated selected healthcare centers and not in retail pharmacies nor in any other facilities to ensure adequate treatment of HAT patients (g-HAT and r-HAT) by HCPs educated to fexinidazole, hence limiting the risk of an inappropriate use, or inadequate supervision and follow-up associated with fexinidazole administration.
Target audience and planned distribution path	Healthcare professional working in dedicated Healthcare centers as selected by the NSSCPs.
Plans to evaluate the effectiveness of the interventions and criteria for success	Fexinidazole will be distributed following the same procedure in place for the distribution of current HAT treatments (NECT, pentamidine, melarsoprol, suramin), ie, through the WHO neglected tropical diseases department to NSSCPs and from there to the treatment centers. In more details, the centers treating HAT patients (g-HAT and r-HAT) report the number of diagnosed cases and their need for products to the NSSCP for national consolidation; this data is then transferred to the WHO local office. Each national WHO office reports the data to the WHO headquarters (Geneva), where final consolidation takes place based on the number of cases reported and subsequent treatment needs. The WHO Geneva then holds regular forecasting meetings with drug manufacturers (Sanofi and Bayer) for initiating manufacturing of the requested batches to finally supply the finished products to MSF Logistiques at Bordeaux, France. Under control and supervision by WHO Geneva, MSF ships the products to each country, where the WHO local office receives the shipment and takes care of clearing customs. Once in the country, NSSCP takes over and distributes the products to each of the treating centers, based on their previously declared needs. Products are stored at each center and are only used under trained HCP supervision and for treating patients. Other effectiveness of this risk minimization measure will be assessed by routine (for g-HAT and r-HAT) and additional pharmacovigilance practices (for g-HAT). As commented in the Controlled access program table above, the pharmacovigilance activities will be set up by WHO.
Guide for healthcare staff (visual aid)	
Objectives	To help HCPs to inform their patients/accompanying person on how to take fexinidazole and give recommendations/guidance in case of adverse events (see [Annex 6]). The key messages of this guide are visual in order to facilitate and ensure the understanding of patient population that may be poorly educated.

	This additional measure is addressing the safety concerns: psychiatric events and vomiting but also provide recommendations on the method of product administration. This guide also includes recommendations for patients on the treatment care.
Rationale for the additional risk minimization activity	Need to provide simplified (visual) information to poor educated patients/accompanying person and ensure a clear understanding on the mode of administration and guidance in case of adverse events.
Target audience and planned distribution path	Health care professional working in dedicated Healthcare centers as defined by the NSSCPs.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of this risk minimization measure will be assessed by routine and additional pharmacovigilance practices. As commented in the Controlled access program table above the pharmacovigilance activities will be set up by WHO. Pharmacovigilance cases will be forwarded to Sanofi Pharmacovigilance by WHO. The guides to be used which are appended to [Annex 6] of this RMP are the ones currently used in the completed clinical study FEX-09. Effectiveness of this HCP guide: Tested in patients treated with fexinidazole in the completed clinical study (study FEX09 -cohort study effectiveness and tolerability of fexinidazole administered to in- or out-patients with stage 1 or 2 HAT due to *T. b. gambiense*). The guides are still adequate to address the important identified or potential risks of fexinidazole use. No update based on the FEX-09 is required.
Patient guide (visual)	
Objectives	To provide a simplified (visual) guidance to patients/accompanying person on the mode of administration of fexinidazole (see [Annex 6]). The key messages of this guide are visual in order to facilitate and ensure the understanding of patient population that may be poorly educated.
Rationale for the additional risk minimization activity	Need to provide simplified information to poor educated patients/accompanying person and ensure a clear understanding on the mode of administration.
Target audience and planned distribution path	Patients/accompanying person will receive this guide via the HCPs working in the specialized health centers, as defined by the NSSCPs.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of this risk minimization measure will be assessed by routine pharmacovigilance practices. As commented in the Controlled access program table above the pharmacovigilance activities will be set up by WHO. Pharmacovigilance cases will be forwarded to Sanofi pharmacovigilance by WHO. The guides to be used which are appended to [Annex 6] of this RMP are the ones used in the completed clinical study FEX-09. Effectiveness of this patient guide: Tested in patients treated with fexinidazole (completed study FEX09 - cohort study effectiveness and tolerability of fexinidazole administered to in- or out-patients with stage 1 or 2 HAT due to *T. b. gambiense*). The guides are still adequate to address the important identified or potential risks of fexinidazole use. No update based on the FEX-09 is required.

AE: Adverse Event; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; HCP: Healthcare Professional; MSF: Medecines Sans Frontieres; NECT: Nifurtimox-Eflornithine Combination Therapy; NSSCP: National Sleeping Sickness Control Program; r-HAT: *Rhodesiense* Human African Trypanosomiasis; RMP: Risk Management Plan; WHO: World Health Organization.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

The risk minimization strategy for fexinidazole includes both routine and additional risk minimization measures, and routine pharmacovigilance activities.

More particularly the additional risk minimization measures consist in a comprehensive program, including a controlled access program, controlled distribution and educational program.

A controlled access program has been organized for minimizing the significant public health and individual patient impact of sleeping sickness in endemic countries. Fexinidazole is not available without such a program as patient access is contingent on fulfilling specific requirements that ensure its safe use. Conjointly with this program, a controlled distribution system has been set up to ensure that distribution fexinidazole is restricted to selected health facilities, and its use reserved to HCPs trained by the NSSCPs in collaboration with WHO. Therefore, both these programs assure the safe use of fexinidazole in HAT patients (g-HAT and r-HAT) by HCPs trained to the use of fexinidazole.

Table 40 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Psychiatric events[a]	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.4, 4.7 and 4.8 of the SmPC. • PL: Labeled in sections 2 and 4 of the PL. **Additional risk minimization measures:** • Guide for healthcare staff (visual aid). • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Vomiting	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.2 and 4.8 of the SmPC. • PL: Labeled in sections 3 and 4 of the PL. **Additional risk minimization measures:** • Guide for healthcare staff (visual aid). • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pro-arrhythmic effect	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC. • PL: Labeled in sections 2 and 4 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Severe infection secondary to drug-induced neutropenia	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.4 and 4.8 of the SmPC. • PL: Labeled in sections 2 and 4 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.3, 4.4 and 5.1 of the SmPC. • PL: Labeled in sections 2 and 4 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[b]	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.5 and 5.2 of the SmPC. • PL: Labeled in section 2 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of

Safety concern	Risk minimization measures	Pharmacovigilance activities
		fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Development of resistance to fexinidazole (For *T. b. gambiense* and *T. b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T. b. gambiense* HAT indication only)	**Routine risk minimization measures:** SmPC: Labeled in section 5.1 of the SmPC. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Use in pregnancy/lactation	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.6 and 5.3 of the SmPC. • PL: Labeled in section 2 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT)**:** Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Use in children <6 years old or less than 20 kg	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.1 and 4.2 of the SmPC. • PL: Labeled in section 2 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

b Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CS: Cockayne Syndrome; CYP: Cytochrome P450; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; HCP: Healthcare Professional; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for FEXINIDAZOLE WINTHROP (Fexinidazole)

This is a summary of the risk management plan (RMP) for FEXINIDAZOLE WINTHROP. The RMP details important risks of FEXINIDAZOLE WINTHROP how these risks can be minimized, and how more information will be obtained about FEXINIDAZOLE WINTHROP's risks and uncertainties (missing information).

FEXINIDAZOLE WINTHROP's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how FEXINIDAZOLE WINTHROP should be used.

This summary of the RMP for FEXINIDAZOLE WINTHROP should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of FEXINIDAZOLE WINTHROP's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Fexinidazole is authorized for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) of HAT due to *Trypanosoma brucei gambiense* in adults and children ≥6 years old and weighing ≥20 kg. (see SmPC for the full indication). Fexinidazole is proposed for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) HAT due to *T. b rhodesiense* in adults and children ≥6 years old and weighing ≥20 kg. It contains fexinidazole as the active substance and it is given orally.

Further information about the evaluation of FEXINIDAZOLE WINTHROP's benefits can be found in FEXINIDAZOLE WINTHROP's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/fexinidazole-winthrop-h-w-2320

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of FEXINIDAZOLE WINTHROP, together with measures to minimize such risks and the proposed studies for learning more about FEXINIDAZOLE WINTHROP's risks, are outlined in the next sections.

Measures to minimize the risks identified for FEXINIDAZOLE WINTHROP include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging (see [Annex 6]);
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly; for FEXINIDAZOLE WINTHROP the pack contains the exact number of tablets for the total duration of treatment (10 days), (see [Annex 6]).
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks. FEXINIDAZOLE WINTHROP can only be prescribed by a trained doctor after having considered the patient can take this medicine.

Together, these measures constitute routine risk minimization measures.

In the case of FEXINIDAZOLE WINTHROP, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of FEXINIDAZOLE WINTHROP is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of FEXINIDAZOLE WINTHROP are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FEXINIDAZOLE WINTHROP. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, use in pregnant/lactating women);

Table 41 - List of important risks and missing information

Important identified risks	Psychiatric events[a]
	Vomiting
Important potential risks	Pro-arrhythmic effect
	Severe infection secondary to drug-induced neutropenia
	Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)

	Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[b]
	Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)
Missing information	Use in pregnancy/lactation
	Use in children <6 years old or less than 20 kg

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

b Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CS: Cockayne Syndrome; CYP: Cytochrome P450; HAT: Human African Trypanosomiasis.

II.B Summary of important risks

Table 42 - Important identified risks with corresponding risk minimization activities and additional pharmacovigilance activities: Psychiatric events

Important Identified risk: Psychiatric events[a]	
Evidence for linking the risk to the medicine	Nitroimidazole class effect HAT studies Chagas study
Risk factors and risk groups	Increased risk of serious psychiatric events in patients with psychiatric disorders (history or acute).
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.4, 4.7 and 4.8 of the SmPC. • PL: Labeled sections 2 and 4 of the PL. **Additional risk minimization measures**: • Guide for healthcare staff (visual aid). • Controlled access program. • Controlled distribution.
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety, suicidal ideation.

HAT: Human African Trypanosomiasis; g-HAT: *Gambiense* Human African Trypanosomiasis; HCP: Healthcare Professional; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 43 - Important identified risks with corresponding risk minimization activities and additional pharmacovigilance activities: Vomiting

Important identified risk: Vomiting	
Evidence for linking the risk to the medicine	Nitroimidazole class effect HAT studies Chagas study

Important identified risk: Vomiting	
Risk factors and risk groups	Increased risk in children.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.2 and 4.8 of the SmPC. • PL: Labeled in sections 3 and 4 of the PL. **Additional risk minimization measures:** • Guide for healthcare staff (visual aid). • Controlled access program. • Controlled distribution.
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

HAT: Human African Trypanosomiasis; g-HAT: *Gambiense* Human African Trypanosomiasis; HCP: Healthcare Professional; PL: Package Leaflet; NSSCP: National Sleeping Sickness Control Program; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 44 - Important potential risks with corresponding risk minimization activities and additional pharmacovigilance activities: Pro-arrhythmic effect

Important potential risk: Pro-arrhythmic effect	
Evidence for linking the risk to the medicine	Non-clinical hERG data: fexinidazole M2 induced significant inhibition. Clinical data.
Risk factors and risk groups	Patients with known congenital prolongation of QTc interval, uncorrected electrolyte abnormalities (eg, hypokalemia or hypomagnesemia), history of symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure or family history of sudden death. Concomitant use of medicinal products that prolong QT interval induce bradycardia or hypokalemia: • Anti-arrhythmics class IA (eg, quinidine, hydroquinidine, disopyramide). • Anti-arrhythmics class III (eg, amiodarone, sotalol, dofetilide, ibutilide). • Tricyclic antidepressive agents (eg, imipramine, amitriptyline). • Certain antimicrobial including some and antituberculosis agents (saquinavir, atazanavir, erythromycin IV, sparfloxacin, moxifloxacin, ofloxacin, levofloxacin, clofazimine, delamanid, pentamidine, certain antimalarials, particularly halofanterine). • Certain antihistaminics (terfenadine, astemizole, mizolastine). • Others (cisapride, vincamine IV, diphemanil, lithium). • Antipsychotics could be used if required, in hospitalized patients under close monitoring.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC. • PL: Labeled sections 2 and 4 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.

Important potential risk: Pro-arrhythmic effect	
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

g-HAT: *Gambiense* Human African Trypanosomiasis; hERG: human Ether-a-go-go-Related Gene; IV: Intravenous; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 45 - Important potential risks with corresponding risk minimization activities and additional pharmacovigilance activities: Severe infection secondary to drug-induced neutropenia

Important potential risk: Severe infection secondary to drug-induced neutropenia	
Evidence for linking the risk to the medicine	Decrease in neutrophil count observed in a few patients in the clinical studies.
Risk factors and risk groups	Human African trypanosomiasis patients with evidence, or history, of blood dyscrasia.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.4 and 4.8 of the SmPC. • PL: Labeled sections 2 and 4 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 46 - Important potential risks with corresponding risk minimization activities and additional pharmacovigilance activities: Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)

Important potential risk: Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)	
Evidence for linking the risk to the medicine	Increase in transaminase observed in some patients treated with fexinidazole in the Chagas study: Evidence effect of cumulative metabolite M2 exposure.
Risk factors and risk groups	Patients with clinical signs of cirrhosis or jaundice.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.3, 4.4 and 5.1 of the SmPC. • PL: Labeled sections 2 and 4 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.

Important potential risk: Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)	
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human African trypanosomiasis: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019

CS: Cockayne Syndrome; g-HAT: *Gambiense* Human African Trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 47 - Important potential risks with corresponding risk minimization activities and additional pharmacovigilance activities: Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19

Important potential risk: Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[a]	
Evidence for linking the risk to the medicine	Sanofi ICH0106 study and INT15307 study.
Risk factors and risk groups	None
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.5 and 5.2 of the SmPC. • PL: Labeled section 2 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019

a Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CYP: Cytochrome P450; g-HAT: *Gambiense* Human African Trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 48 - Important potential risks with corresponding risk minimization activities and additional pharmacovigilance activities: Development of resistance to fexinidazole (For *T.b. gambiense* and *T. b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T. b. gambiense* HAT indication only)

Important potential risk: Development of resistance to fexinidazole (For *T. b. gambiense* and *T. b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T. b. gambiense* HAT indication only)	
Evidence for linking the risk to the medicine	Multiple researches on nitroimidazole resistance induction in trypanosomes. (29)
Risk factors and risk groups	As for other drug resistance, the risk factors could be related to incomplete treatment, inappropriate use of the compound, and repeated exposure to the treatment. Human African Trypanosomiasis patients treated with nitro imidazole compounds or off-label.

Important potential risk: Development of resistance to fexinidazole (For *T. b. gambiense* and *T. b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T. b. gambiense* HAT indication only)	
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in section 5.1 of the SmPC. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 49 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in pregnancy/lactation

Missing Information: Use in pregnancy/lactation	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.6 and 5.3 of the SmPC. • PL: Labeled section 2 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.
Additional pharmacovigilance activities	FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.

g-HAT: *Gambiense* Human African Trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; PL: Package Leaflet; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

Table 50 - Missing information with corresponding risk minimization activities: Use in children <6 years old or less than 20 kg

Missing Information: Use in children <6 years old or less than 20 kg	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.1 and 4.2 of the SmPC. • PL: Labelled in section 2 of the PL. **Additional risk minimization measures:** • Controlled access program. • Controlled distribution.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of FEXINIDAZOLE WINTHROP.

II.C.2 Other studies in post-authorization development plan

Table 51 - Other studies in post-authorization development plan

FEXINC09395 (for g-HAT)
Study short name and title
Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Rationale and study objectives
Rationale
Fexinidazole is a new treatment modality to be prescribed for the treatment of HAT in countries where the local pharmacovigilance system may be poorly organized. As was done for NECT (31) a close pharmacovigilance process will be implemented. Additionally, this will ensure that adequate supervision is maintained for patients taking treatment at home.
Data collection of fexinidazole-treated HAT patients in the NSSCP has been endorsed by PRAC on 26-Jun-2018.
The study can be considered as an additional pharmacovigilance activity and should be included in the pharmacovigilance plan as a category 3 PASS.
Study objectives
The primary objective of this post-authorization safety study will be to assess the safety of fexinidazole in field conditions of use.
The secondary objective will be to describe the effectiveness of fexinidazole, in real-life use by evaluating occurrence of relapse at 12 and 24 months of follow-up.

AUC: Area Under Curve; C_{max}: Maximum Plasma Concentration; CYP: Cytochrome; DDI: Drug-Drug Interaction; HAT: Human African Trypanosomiasis; NECT: Nifurtimox-Eflornithine Combination Therapy; NSSCP: National Sleeping Sickness Control Program; PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee.

REFERENCES

1. Institute for Health Metrics and Evaluation [Internet]. GBD Data Explorer, Seattle, WA: IHME, University of Washington, 2019 [cited 2021 Feb 06]. Available from: https://clients.ihme.services/data-explorer

2. Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, Grout L, et al. Monitoring the elimination of human African trypanosomiasis at continental and country level: Update to 2018. PLoS Negl Trop Dis. 2020 May 21;14(5):e0008261.

3. World Health Organization [Internet]. Trypanosomiasis, human African (sleeping sickness) - Key facts; [cited 2022 Jan]. Available from: https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)

4. World Health Organization [Internet]. Global Health Observatory data repository. Number of new reported cases (T.b. gambiense) Data by country; [cited 2022 Jul 21]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/hat-tb-gambiense

5. World Health Organization [Internet]. Global Health Observatory data repository. Number of new reported cases (T.b. rhodesiense) Data by country; [cited 2022 Jul 21]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/number-of-new-reported-cases-of-human-african-trypanosomiasis-(t-b-rhodesiense)

6. Franco JR, Cecchi G, Paone M, Diarra A, Grout L, Kadima Ebeja A, et al. The elimination of human African trypanosomiasis: Achievements in relation to WHO road map targets for 2020. PLoS Negl Trop Dis. 2022 Jan 18;16(1):e0010047.

7. World Health Organization [Internet]. WHO communication. Sleeping sickness elimination progresses in 2021 despite COVID-19; [2022 May; accessed 2023 Jan 03]. Available from: https://www.who.int/news/item/30-05-2022-sleeping-sickness-elimination-progresses-in-2021-despite-covid-19

8. Franco JR, Cecchi G, Priotto G, Paone M, Kadima Ebeja A, Simarro PP, et al. Human African trypanosomiasis cases diagnosed in non-endemic countries (2011-2020). PLoS Negl Trop Dis. 2022 Nov 7;16(11):e0010885.

9. World Health Organization [Internet]. WHO Report series 984 Control and surveillance of human african trypanosomiasis; 2013. [cited 2016 Nov 15]. Available from: http://apps.who.int/iris/bitstream/10665/95732/1/9789241209847_eng.pdf?ua=1

10. Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, et al. Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet. 2009 Jul 4;374(9683):56-64.

11. World Health Organization [Internet]. WHO guidelines. [accessed 2023 Jan 18]. Available from: https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)

12. Centers for Disease Control and Prevention [Internet]. Availbale from: https://www.cdc.gov/parasites/sleepingsickness/health_professionals/index.html

13. MSF medical guidelines. Clinical guidelines - Diagnosis and treatment manual. Parasitic diseases. Chapter 6. 2022 Nov. p. 125-126

14. World Health Organization. Control and surveillance of human African trypanosomiasis. World Health Organ Tech Rep Ser. 2013;(984):1-237.

15. Kotepui KU, Masangkay FR, De Jesus Milanez G, Kotepui M. Prevalence and outcomes of malaria as co-infection among patients with human African trypanosomiasis: a systematic review and meta-analysis. Sci Rep. 2021 Dec 10;11(1):23777.

16. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. Int J Epidemiol. 2014 Apr;43(2):476-93.

17. Erskine HE, Baxter AJ, Patton G, Moffitt TE, Patel V, Whiteford HA, et al. The global coverage of prevalence data for mental disorders in children and adolescents. Epidemiol Psychiatr Sci. 2017 Aug;26(4):395-402.

18. Centers for Disease Control and Prevention [Internet]. Mental Health Home Mental Health Basics Burden of Mental Illness. 2013. Available from: https://www.cdc.gov/mentalhealth/basics/burden.htm

19. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015 Mar;56(3):345-65.

20. De Souza Lopes C, Robaina JR, Rotenberg L. Epidemiology of insomnia: prevalence and risk factors. In Can't sleep. 2012 Mar 14:1-21. Available from: http://www.intechopen.com/books/can-t-sleep-issuesof-being-an-insomniac/epidemiology-of-insomnia-prevalence-and-risk-factors

21. Blum JA, Burri C, Hatz C, Kazumba L, Mangoni P, Zellweger MJ. Sleeping hearts: the role of the heart in sleeping sickness (human African trypanosomiasis). Trop Med Int Health. 2007 Dec;12(12):1422-32.

22. Blum JA, Schmid C, Burri C, Hatz C, Olson C, Fungula B, et al. Cardiac alterations in human African trypanosomiasis (T.b. gambiense) with respect to the disease stage and antiparasitic treatment. PLoS Negl Trop Dis. 2009;3(2):e383.

23. Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. Europace. 2014 Jan;16(1):101-8.

24. Mantzaris I, Msaouel P, Lam A.P, Friedman EW, Yu Y, Verma A. Ethnicity Specific Cutoffs for Neutropenia Are Predictive of Overall Survival in a Large Elderly Cohort: An Analysis of 26,652 Individuals. Blood J. 2014;124(21).

25. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Ann Intern Med. 2007 Apr 3;146(7):486-92.

26. Checchi F, Piola P, Ayikoru H, Thomas F, Legros D, Priotto G. Nifurtimox plus Eflornithine for late-stage sleeping sickness in Uganda: a case series. PLoS Negl Trop Dis. 2007 Nov 7;1(2):e64.

27. Priotto G, Kasparian S, Ngouama D, Ghorashian S, Arnold U, Ghabri S, at al. Nifurtimox-eflornithine combination therapy for second-stage Trypanosoma brucei gambiense sleeping sickness: a randomized clinical trial in Congo. Clin Infect Dis. 2007 Dec 1;45(11):1435-42.

28. Priotto G, Fogg C, Balasegaram M, Erphas O, Louga A, Checchi F, et al. Three drug combinations for late-stage Trypanosoma brucei gambiense sleeping sickness: a randomized clinical trial in Uganda. PLoS Clin Trials. 2006 Dec 8;1(8):e39.

29. Sokolova AY, Wyllie S, Patterson S, Oza SL, Read KD, Fairlamb AH. Cross-resistance to nitro drugs and implications for treatment of human African trypanosomiasis. Antimicrob Agents Chemother. 2010 Jul;54(7):2893-900.

30. Barrett MP, Vincent IM, Burchmore RJ, Kazibwe AJ, Matovu E. Drug resistance in human African trypanosomiasis. Future Microbiol. 2011 Sep;6(9):1037-47.

31. Franco JR, Simarro PP, Diarra A, Ruiz-Postigo JA, Samo M, Jannin JG. Monitoring the use of nifurtimox-eflornithine combination therapy (NECT) in the treatment of second stage gambiense human African trypanosomiasis. Res Rep Trop Med. 2012 Aug 23;3:93-101.

32. Lindner AK, Lejon V, Chappuis F, Seixas J, Kazumba L, Barrett MP, et al. New WHO guidelines for treatment of gambiense human African trypanosomiasis including fexinidazole: substantial changes for clinical practice. Lancet Infect Dis. 2020 Feb;20(2):e38-e46.

RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL MINIMIZATION ACTIVITIES

Approved key messages of the additional risk minimization measures

Prior to the launch of FEXINIDAZOLE WINTHROP in target countries, the scientific opinion holder must agree the content and format of the controlled access programme, the controlled distribution system, and the educational programme, including communication media and distribution modalities, with the National Competent Authority. The controlled access programme, the controlled distribution system, and the educational programme are aimed at ensuring that patients are informed on the safe use of the medicine, and that they are supervised by trained health care staff. The scientific opinion holder shall ensure that in each country where FEXINIDAZOLE WINTHROP is marketed, all healthcare staff and patients/carers who will use FEXINIDAZOLE WINTHROP have access to/are provided with the following educational package:

1. Healthcare staff educational material
2. Patient information pack

- Healthcare staff educational material:

  The Summary of Product Characteristics

  Guide for healthcare staff (visual aid)

Key messages for the Guide for healthcare staff:

- That the healthcare staff should instruct the patients/carers on how FEXINIDAZOLE WINTHROPshould be taken, and give guidance in case of adverse events;
- That there is a risk of psychiatric events when using the medicine they need to be aware of;
- It should advise the healthcare staff how to continue the treatment after repeated events of patient vomiting;
- That the healthcare staff should convey to the patients/carers the importance of contacting them in the case of a second event of vomiting;
- That the healthcare staff should monitor the completion of the treatment.

- The patient information pack:
  - A patient/carer guide (visual aid)

Key messages for the Patient/carer guide:

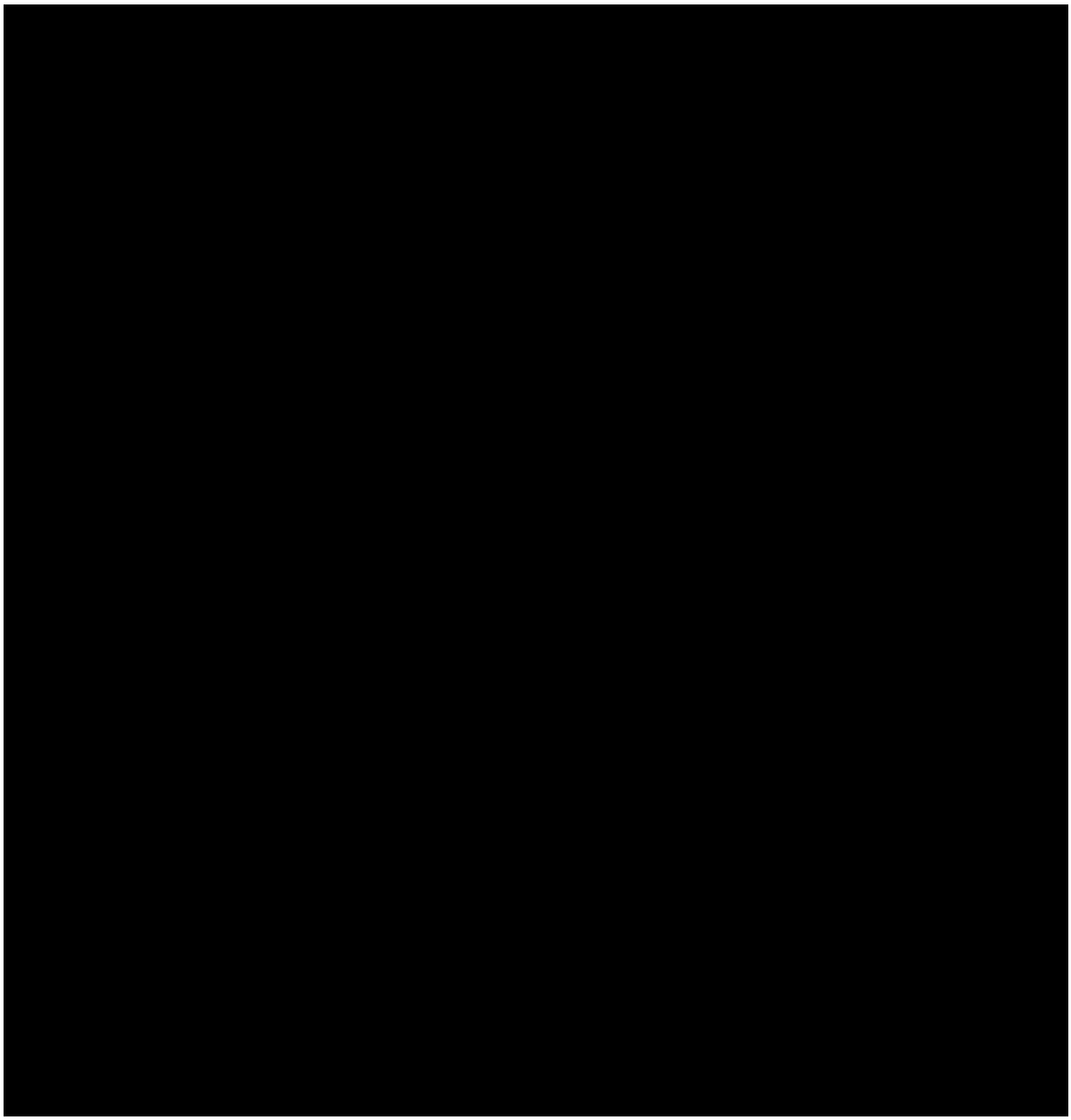
- Mode of administration of FEXINIDAZOLE WINTHROP;
- That the treatment will be initiated and supervised by a trained healthcare staff.

Annex 6.1: Fexinidazole package
Annex 6.2: Healthcare professional (HCP) visual guide
Annex 6.3: Patient guide adult
Annex 6.4: Patient guide child

Fexinidazole package for 2 patients- Adult and Child

Package - Adult

Package – Child



GUIDE FOR OUTPATIENTS