ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fexinidazole Winthrop 600 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg fexinidazole.

Excipient with known effect:
Each tablet contains 115.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Pale yellow, round, 13 mm diameter, biconvex tablet debossed with “4512” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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. Fexinidazole should be used in line with official recommendations (see section 4.4).

4.2 Posology and method of administration

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) (see section 4.4 for selection of patients for treatment with fexinidazole and the need for hospitalisation during treatment with fexinidazole).

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 1 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 (see section 4.8).
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 (see section 5.2).
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.

Special populations

Paediatric population
The safety and efficacy of Fexinidazole Winthrop in children aged less than 6 years and/or with less than 20 kg in body weight have not been established. No data are available.

Elderly population
No dose adjustment is required in patients aged ≥ 65 years (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
There is limited clinical data in patients with hepatic impairment. In patients with mild or moderate hepatic impairment (Child-Pugh A or B), mild changes in exposure of fexinidazole and active metabolites may occur. No dosage adjustment is needed but fexinidazole should be used with caution in these patients (see sections 4.4 and 5.2). Fexinidazole is contraindicated in patients with severe hepatic impairment (Child-Pugh C or signs and symptoms of hepatic decompensation such as jaundice, pruritus, ascites, upper gastrointestinal bleeding), (see section 4.3).

Method of administration

Oral use.

The tablets should be taken with food. The tablets should not be broken or crushed.

4.3 Contraindications

Hypersensitivity to fexinidazole, to any agent of the nitroimidazole class (e.g. metronizadole, tinidazole), or to any of the excipients (see section 6.1).

Patients with severe hepatic impairment (Child-Pugh C or signs and symptoms of hepatic decompensation such as jaundice, pruritus, ascites, upper gastrointestinal bleeding), (see sections 4.2, 4.4 and 5.2).

Patients at risk of QT interval prolongation: patients with congenital prolongation of QT interval, uncorrected electrolyte abnormalities (e.g. hypokalaemia or hypomagnesaemia), history of symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure, family history of sudden death or patients with concomitant use of medicinal products that prolong QT interval, induce bradycardia or hypokalaemia (see sections 4.4 QT interval prolongation, 4.5 and 4.8).

4.4 Special warnings and precautions for use

Selection of patients with g-HAT for treatment with fexinidazole

Lower efficacy of fexinidazole as compared to nifurtimox-eflornithine combination therapy (NECT) has been seen in a subgroup of patients (see section 5.1).

Patients with cerebrospinal fluid white blood cells count (CSF-WBC) >100/µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated.

Hospitalisation during treatment course

In patients where there is risk of poor compliance to the recommended fexinidazole regimen, in children with a body weight lower than 35 kg (see section 5.2) and in patients with psychiatric disorders (history or acute) (see neuropsychiatric adverse reactions), hospitalized administration of Fexinidazole Winthrop should be done under the strict supervision of trained health staff. The same applies to the exceptional cases where severe patients with g-HAT and CSF-WBC > 100/µL cannot be treated with any other adequate treatment (e.g. NECT).

Risk of relapse

In g-HAT, as the risk of relapse is higher after fexinidazole treatment as compared to NECT (see section 5.1), patients should have follow-up monitoring at recurrence of symptoms suggestive of HAT, at 12 months and up to 24 months after treatment completion with fexinidazole.
In r-HAT, efficacy data of fexinidazole including on risk of relapse are limited (see section 5.1). Patients treated with fexinidazole should be monitored for 12 months for recurrence of symptoms suggestive of HAT. Patients should be made aware of the risk of relapse after therapy and instructed to contact the healthcare staff in case of signs of relapse.

QT interval prolongation

In the g-HAT pivotal clinical study, cases of QTcF interval increase were reported in patients treated with fexinidazole, with an average increase of 15.4 ms (see section 4.8).
Fexinidazole is contraindicated in at risk patients with known congenital prolongation of QT interval, uncorrected electrolyte abnormalities (e.g. hypokalaemia or hypomagnesemia), history of symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure, or family history of sudden death, as this may lead to an increased risk for ventricular arrhythmias.

In order to compensate for potential hypokalaemia in a patient with malnutrition or diarrhoea/vomiting, the patient should receive potassium-rich foods or potassium chloride tablets.

Co-administration of fexinidazole is contraindicated with the following QT-interval prolonging medicinal products (see section 4.5):
- Anti-arrhythmics class IA and III
- Tricyclic antidepressive agents
- Certain antimicrobial agents
- Certain antihistaminics
- Others

In addition, co-administration of fexinidazole is contraindicated with medicinal products that can reduce potassium levels or are associated with clinically significant bradycardia (see section 4.5).
If patients are, or need to be treated with medicinal products known to prolong QT interval or to induce bradycardia or hypokalaemia, either do not initiate fexinidazole until such medicinal products are eliminated from the body (allow a washout period of 5 half-lives), or do not start such medicinal products until fexinidazole and its active metabolites are eliminated from the body (allow a washout period of 7 days).

Neuropsychiatric adverse reactions

Adult patients treated with fexinidazole in the g-HAT pivotal study reported a higher percentage of neuropsychiatric adverse reactions, including suicidal ideation, than those treated with nifurtimox eflornithine combination therapy (NECT) (see section 4.8). Patients and their relatives should be advised to contact their doctor immediately if they notice signs of suicidal ideation. 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 hospitalised during the 10-day treatment period.

Severe infection

Neutropenia may occur in patients receiving fexinidazole. Therefore, fexinidazole should be used with caution in patients with evidence, or history, of blood dyscrasia. Patients should return to the clinic if they develop a fever or clinical signs of suspected infection within 3 months of the end of treatment.

Hepatic impairment and potential for hepatotoxicity

Fexinidazole is extensively metabolised in the liver to generate active metabolites. There is limited experience of use in patients with hepatic impairment (see section 5.2). The use of fexinidazole is contraindicated in patients with severe hepatic impairment (Child-Pugh C or signs and symptoms of hepatic decompensation such as jaundice, pruritus, ascites, upper gastrointestinal bleeding), and it should be used with caution in patients with mild and moderate hepatic impairment (Child-Pugh A or B).
Reversible elevations of liver transaminases may occur in patients receiving fexinidazole.
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. In this population, 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.

Severe renal impairment

No data are available in patients with severe renal impairment. Caution should be exercised when administering fexinidazole to these patients.

Elderly patients

Limited data are available in patients aged 65 years and over. Caution should be exercised when administering fexinidazole to the elderly.

Alcohol
Alcohol should not be consumed during treatment with fexinidazole or within 48 hours of the last dose due to the risk of a disulfiram-like reaction (antabuse effect) characterized by flushing, rash, peripheral oedema, nausea and headache (see section 4.5).

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

- Due to pharmacodynamic interactions, the following concomitant uses are contraindicated (see sections 4.3 and 4.4):

- Medicinal products that may prolong the QT interval: concomitant use of fexinidazole and the following medicinal products is contraindicated because the risk of an additive effect on QT interval prolongation cannot be excluded.
- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- tricyclic antidepressive agents (e.g. imipramine, amitriptyline)
- certain antimicrobials including some antituberculosis agents (saquinavir, atazanavir, erythromycin IV, sparfloxacin, moxifloxacin, ofloxacin, levofloxacin, clofazimine, delamanid, pentamidine, certain antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, diphemanil, lithium).

Antipsychotics could be used if required, in hospitalised patients under close monitoring (see section 4.4 Neuropsychiatric adverse reactions)

- Medicinal products that may lead to proarrhythmic events: concomitant use is contraindicated with medicinal products that can reduce potassium levels (loop and thiazide diuretics, laxatives and enemas at high doses, corticosteroids, amphotericin B) or are associated with clinically significant bradycardia (beta-blockers, calcium channel blockers), as it may lead to an increased risk of proarrhythmic events.

If patients are, or need to be treated with medicinal products known to prolong QT interval or to induce bradycardia or hypokalaemia, either do not initiate fexinidazole until such medicinal products are eliminated from the body (allow a washout period of 5 half-lives), or do not start such medicinal products until fexinidazole and its active metabolites are eliminated from the body (allow a washout period of 7 days).

- Due to potential pharmacodynamic interactions, the following concomitant uses are not recommended:

- Disulfiram: cases of psychotic reactions have been reported after the concomitant administration of 5-nitroimidazoles (benznidazole and metronidazole) with disulfiram. Because this effect cannot be ruled out for fexinidazole, disulfiram should not be used concomitantly with fexinidazole.

- Alcohol: alcohol should not be consumed during treatment of fexinidazole or within 48 hours of the last dose (see section 4.4).

- Propylene glycol: as 5-nitroimidazoles interfere with the metabolism of propylene glycol, this effect could not be ruled out for fexinidazole. Medicinal products containing propylene glycol should not be used concomitantly with fexinidazole.

- Traditional medicines: it is recommended to avoid the use of traditional or herbal medicines during the entire treatment with fexinidazole, as the potential interactions are unknown.

Pharmacokinetic interactions

Effect of other medicinal products on fexinidazole

Since no *in vivo* drug interaction studies with CYP3A4 inhibitors or CYP3A4 inducers were performed, it is recommended to not administer CYP3A4 potent inhibitors or CYP3A4 potent inducers with fexinidazole. Based on the metabolism pathway (see section 5.2), only a limited interaction is predicted between CYP3A4 inhibitors and fexinidazole. This is predicted to have only a limited impact on exposure to fexinidazole, M1 and M2. It is unlikely that CYP3A4 inducers could modify the efficacy of fexinidazole.

The following medicinal products have been concomitantly administered in a limited number of patients in the clinical trials without an effect on the pharmacokinetic parameters of fexinidazole and the M1 and M2 metabolites: paracetamol, and the following CYP2D6 inhibitors: chlorpromazine, metoclopramide, artemether-lumefantrine, chloramphenicol, chlorphenamine, cimetidine; this suggests that these medicinal products may be used with caution.

Effect of fexinidazole on other medicinal products

- Medicinal products metabolized by CYP1A2 or CYP2C19: repeated administration of fexinidazole to healthy subjects at the recommended therapeutic dosing regimen increases (around 2-fold) the exposures of probe substrate of CYP1A2 (caffeine) and CYP2C19 (omeprazole). Caution and monitoring of adverse reactions are advised when fexinidazole is concomitantly used with medicinal products which are metabolized by CYP1A2 (such as caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline) or CYP2C19 (such as omeprazole, lansoprazole, mephenytoin, diazepam), as it could result in an increase in exposure of these medicinal products.

- Medicinal products metabolized by CYP3A4/5: Decreased concentrations resulting in decreased efficacy of medicinal products highly metabolized by CYP3A4/5 and with a significant CYP3A4/5 first pass, such as lovastatin, simvastatin, nisoldipine or midazolam may be observed. Caution and monitoring for lack of efficacy are advised when fexinidazole is concomitantly used with such medicinal products.

- Medicinal products metabolized by CYP2B6: fexinidazole induces CYP2B6 mRNA expression *in vitro*. Caution is advised when fexinidazole is concomitantly used with medicinal products which are metabolized by CYP2B6 (such as bupropion, efavirenz), as it could result in a decrease in exposure of these medicinal products.

- Medicinal products substrates of OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K transporters: fexinidazole, M1 and/or M2, inhibit OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K transporters *in vitro*. It is predicted that, *in vivo*, fexinidazole could increase the exposures of medicinal products which are substrates of OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K transporters, such as metformin, dofetilide, adefovir, cefaclor and furosemide. Caution and monitoring of adverse reactions are advised when fexinidazole is concomitantly used with such medicinal products as it could result in an increase in exposure of these medicinal products (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of fexinidazole in pregnant women.
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 section 5.3). 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.

Breast-feeding

There are no data from the use of fexinidazole in breast-feeding women. Available pharmacokinetic data in rats have shown that fexinidazole and its two active metabolites are excreted into breast milk (see section 5.2). Effects on suckling rat pups were limited to transient development retardation at a sub-clinical exposure level. As a risk to the suckling child cannot be excluded, 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.

Fertility

In animal studies, no effects on fertility and reproductive performance were observed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Dizziness, fatigue, asthenia and somnolence have been reported following treatment with fexinidazole.

4.8 Undesirable effects

Summary of the safety profile

The safety of Fexinidazole Winthrop (oral once daily for 10 days) in the treatment of *T. b. gambiense* HAT has been evaluated in three clinical trials: Study DNDiFEX004 compared fexinidazole (N=264) to oral nifurtimox and intravenous eflornithine (NECT) in late stage 2 HAT patients aged from 15 years (N=130). Studies DNDiFEX005 and DNDiFEX006 were uncontrolled and conducted in patients aged from 15 years with stage 1 and early stage 2 HAT (N=230) and in children aged 6 years to 15 years with any stage HAT (N=125), respectively.

The most frequently reported adverse reactions (considered at least possibly related to treatment) in the pooled g-HAT fexinidazole group (619 patients) were vomiting (38%), nausea (33%), asthenia (20%), decreased appetite (17%), headache (16%), insomnia (15%), tremor (14%), and dizziness (14%).

Tabulated list of adverse reactions in g-HAT

Adverse reactions are presented by system organ class. Frequency categories are defined by using the MedDRA frequency convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000)

Table 2: Adverse Reactions by decreasing frequency reported in at least 2 patients treated with fexinidazole in g-HAT

System Organ Class	Very Common	Common	Uncommon
Blood and lymphatic system disorders		Anaemia, neutropenia	
Metabolism and nutrition disorders	Decreased appetite	Hypocalcaemia, hyperkalaemia, hyponatraemia, hypoalbuminaemia	Hypoglycaemia
Psychiatric disorders	Insomnia	Hallucination, agitation, logorrhoea, abnormal behaviour, anxiety, psychotic disorder	Depression, suicidal ideation, nightmare, personality change, acute psychosis, delirium, euphoric mood, mental disorder
Nervous system disorders	Headache, tremor, dizziness	Extrapyramidal disorder, paraesthesia	Convulsion, dysgeusia, cerebellar syndrome, dyskinesia, grand mal convulsion, motor dysfunction, psychomotor hyperactivity
Eye disorders		Eye pain, photophobia	Eye pruritus, eyelid oedema
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Palpitations, QT interval prolongation	Tachycardia
Vascular disorders		Hot flush, hypertension	
Respiratory, thoracic and mediastinal disorders		Cough	Dyspnoea, hiccups, oropharyngeal pain
Gastrointestinal disorders	Vomiting, nausea, dyspepsia	Abdominal pain upper, salivary hypersecretion, abdominal pain, gastritis, constipation, dry mouth	Abdominal distension, diarrhoea, dysphagia, eructation, gastrointestinal sounds abnormal
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritus, pruritus generalised
Musculoskeletal and connective tissue disorders		Back pain, neck pain	Myalgia, arthralgia, muscle spasms, musculoskeletal pain, pain in jaw, sensation of heaviness
Renal and urinary disorders			Nocturia, pollakiuria, urinary incontinence
General disorders and administration site conditions	Asthenia	Feeling hot, chest pain, pyrexia, gait disturbance	Chills, fatigue, feeling cold
Investigational		Blood sodium decreased, blood potassium increased	Blood albumin decreased, blood calcium decreased, blood potassium decreased

The safety profile of fexinidazole in an open label, non-randomized trial in 45 patients with stage-1 and stage-2 r-HAT was consistent with the safety profile in g-HAT. QT interval prolongation and vomiting were the most frequently reported adverse reactions in this trial.

Description of selected adverse reactions

- Psychiatric related events
Adult patients treated with fexinidazole for g-HAT reported a higher percentage of psychiatric related events (≥1%), including (by decreasing frequency) insomnia, agitation, anxiety, psychotic disorder, abnormal behaviour, depression, logorrhoea, nightmare, personality change, and suicidal ideation than those treated with NECT in pivotal clinical study (see section 4.4). Most occurred during treatment period with mild to moderate severity, and did not result in treatment discontinuation. Psychiatric related events (≥1%) including (by decreasing frequency) insomnia, hallucination and psychotic disorder were also reported with fexinidazole in paediatric patients. Most were of mild to moderate severity, and did not result in treatment discontinuation.

- QT interval prolongation
In Study DNDiFEX004 in g-HAT, treatment with fexinidazole caused an average increase of 15 to 20 ms in the QTcF interval. Nineteen (7.2%) patients in the fexinidazole group had a QTcF value of > 450 ms (see sections 4.3 and 4.4).

Paediatric population
Paediatric patients showed a similar safety profile to that of the adult population except for more frequent vomiting within 2 hours of administration. Vomiting within 30 minutes of Fexinidazole Winthrop administration occurred in 20% of paediatric population vs. 6.1% of adult patients with g-HAT, with a trend to a higher incidence of vomiting during the loading phase. Events of vomiting were mostly mild to moderate in intensity and did not result in permanent treatment discontinuation.

4.9 Overdose

Healthy subjects were exposed to doses higher than the recommended therapeutic doses. These higher doses were associated with higher rates of increased transaminases, vomiting and panic attack.

One paediatric g-HAT patient received the adult dosing regimen instead of the regimen appropriate to body weight and presented with vomiting over the first 5 days of treatment and increased potassium and decreased calcium levels from Day 11 to Week 9.

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antiparasitic products, antiprotozoals, agents against leishmaniasis and trypanosomiasis, nitroimidazole derivatives

ATC code P01CA03

Mechanism of action

No specific studies have been performed to assess the mechanism of action (MoA) of fexinidazole and the M1 and M2 metabolites.
Non-clinical studies suggest that nitro containing medicinal products, such as fexinidazole, have a common MoA, which involves bioactivation by parasitic nitroreductase enzymes to generate reactive amines that exert indirect toxic and mutagenic effects on the trypanosomes.

In-vitro activity
The trypanocidal effect of fexinidazole and its two metabolites, M1 and M2, has been assessed *in vitro* using a variety of *T. brucei* sub-species and strains. The metabolites were more active than the parent compound, with MICs (lowest concentrations that completely inhibits visible parasite growth) against *T. brucei* parasites of 5.0, 4.74 and 2.20 µg/mL for fexinidazole, M1, and M2, respectively.

In-vivo activity
Fexinidazole was shown to be effective in murine models of acute infection with *T. b. gambiense* and *T. b. rhodesiense*. C_{max} plasma levels of fexinidazole, M1 and M2 in these models were estimated to be around 0.457, 33.6 and 77.6 µg/mL, respectively, after repeat oral dosing with fexinidazole (200 mg/kg/day for 5 days), which are of a similar order to the mean Cmax in humans (0.777, 7.77 and 18.8 µg/mL for fexinidazole, M1 and M2, respectively, on last day of loading dose, Day 4) treated with fexinidazole at the recommended dose regimen.

Cross-resistance
Fexinidazole has shown cross-resistance in *in vitro* and *in vivo* studies using a nifurtimox-resistant *T. b. gambiense*.

Clinical efficacy

Gambiense HAT

DNDiFEX004
This was a randomised, open-label, multicentre, non-inferiority study in patients with late stage 2 (or meningo-encephalitic) HAT due to *T. b. gambiense*. Patients (n=394) were randomized in a 2:1 ratio to a 10-day treatment regimen of either fexinidazole (n=264) or NECT (n=130). The mean age was 35 (range 15 to 71) and 61% were male. The fexinidazole group received 1800 mg of fexinidazole orally once daily for Days 1 through 4, followed by 1200 mg orally once daily for Days 5 through 10, with all dosing in the fed state.

The primary efficacy objective was to demonstrate a non-inferior success rate of fexinidazole to NECT at 18 months after the end of treatment (EOT), with the margin of acceptable difference at 13%. Month 18 success rates were 91.2% for fexinidazole vs. 97.6% for NECT (difference fexinidazole-NECT -6.42%, 97.06% CI [-11.22; -1.61]).
However, in the subpopulation of patients with cerebrospinal fluid white blood count (CSF-WBC) > 100/µL the efficacy was 86.9% in the fexinidazole arm versus 98.7%% in the NECT arm, and therefore the risk of failure was higher in this subgroup with fexinidazole (see table 3).

Table 3: Treatment success at 18 months according to baseline CSF-WBC count

Treatment	WBC count	N	Treatment failure n (%)	Treatment success n (%)
fexinidazole	≤100	102	2 (2.0)	100 (98.0)
	>100	160	21 (13.1)	139 (86.9)
NECT	≤100	49	2 (4.1)	47 (95.9)
	>100	78	1 (1.3)	77 (98.7)

Abbreviations: WBC: White blood cell; CSF: Cerebrospinal fluid; NECT: nifurtimox-eflornithine combination therapy

The differences in relapse rate between fexinidazole treatment and NECT are presented in the table 4:

Table 4: Relapse rates of fexinidazole and NECT

		Number of relapses			
	Set of patients	by12 months (D365)	12 to 18 months (D548)	>18months (D549+)	Total at end of follow-up
Fexinidazole	262	3 (1.15%)	6 (2.29%)	5 (1,9%)	14* (5.3%)
NECT	127	0	0	0	0

1. *A total of 17 patients treated with fexinidazole were initially considered as relapse but 3 were not confirmed at Month 24

DNDiFEX005
This was an open-label, single-arm, multicentre study in patients with stage 1 (n=189) and early stage 2 (n=41) HAT due to *T. b. gambiense*. Fexinidazole was given as in DNDiFEX004. The mean age was 34 (range 15 to 73) and 50% were male. The primary efficacy objective was to demonstrate a fexinidazole success rate greater than 80% at 12 months after the EOT. At Month 12 the overall success rate was 98.7%, 95% CI [96.2; 99.7].

DNDiFEX006
This was an open-label, single-arm, multicentre, cohort study in patients aged 6 to 15 weighing at least 20kg with stage 1 (n=69), early (n=19) or late (n=37) stage 2 HAT due to *T. b. gambiense*. Fexinidazole 1200 mg was given once a day on Days 1 through 4, followed by 600 mg on Days 5 through 10 to patients weighing <35 kg and all other patients received the adult dosing regimen. The primary efficacy objective was to demonstrate a fexinidazole success rate greater than 80% at 12 months after the EOT. The overall success rate at 12 months was 97.6%, 95% CI [93.1; 99.5].

Rhodesiense HAT

DNDiFEX007
This was a phase 2/3, open-label, non-randomized clinical trial of rhodesiense-HAT patients conducted in Malawi and Uganda, which included 45 patients of which 35 stage-2 and 10 stage-1 r-HAT patients. These patients received the same dose regimen as indicated in g-HAT. The low dose was used in 11 patients ≤ 12 years old and < 35 kg. The median age was 24 years. The primary endpoint was the attributable fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EOH) in stage-2 patients treated with fexinidazole. The main secondary endpoints were failure rate at the EOH or after 12 months follow up in stage-1 and stage-2 r-HAT patients.
One patient died but this was considered unrelated to HAT or the treatment. One relapse occurred in a stage-2 patient at week 9. There are no data beyond 12 months of follow-up.

Table 5. Post-hoc analysis of treatment failure including all-cause mortality in intention-to-treat-population.

	End of hospitalisation	**12 months**
Stage 2	2.9% (1/35) (95% CI: 0.07% to 14.9%)	5.7% (2/35) (95% CI: 0.70% to 19.2%)
Stage 1	0% (0/10)	0% (0/10)
Overall (stage 1 and 2)	2.2% (1/45) (95% CI: 0.06% to 11.8%)	4.4% (2/45) (95% CI: 0.5% to 15.2%)

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single 1200 mg dose to fasted healthy adult male volunteers, fexinidazole was rapidly absorbed and extensively metabolised with exposures (C_{max}/AUC_{0-24h}) of metabolites which were 6.76/8.67 (M1) and 6.27/10.4 (M2) - fold higher than that of fexinidazole. Food intake increased markedly the bioavailability of fexinidazole, and subsequent both metabolites, by 2.4 to 3.0 fold. Following oral administration to healthy fed volunteers at the recommended treatment regimen for fexinidazole (1800 mg once daily for four days and then 1200 mg once daily for six days), median peak plasma concentrations were at 4 hours for fexinidazole and M1, and 24 hours for M2 after the first dose, and steady state was reached between 7 and 10 days for all analytes. The exposures of fexinidazole and its metabolites M1 and M2 were comparable between g-HAT and r-HAT patients at the end of the maintenance dose (Day 10).

Distribution

Fexinidazole is highly bound to human serum proteins *in vitro* (95.4%), whereas binding of the active metabolites, M1 and M2, was less at 25.9 and 41.6%, respectively.
In patients with stage 2 HAT treated with fexinidazole, maximum concentrations in the cerebrospinal fluid (CSF) of the metabolites ranged from 0.91 to 1.53 µg/mL for M1, and 6.17 to 7.08 µg/mL for M2, at 24 hours after the last administration on Day 10. The ratio of CSF/plasma concentrations in adult patients was found to be approximately 31% for M2, 52% for M1, and around 50% for both metabolites in children.

Biotransformation

Fexinidazole is extensively metabolized primarily to the sulfoxide metabolite M1, which then is further metabolized to the sulfone metabolite M2. Fexinidazole is metabolised by several CYPs, with a limited contribution of CYP3A4 (*in vitro* fraction metabolized (fm) by CYP3A4: 12%) and by several flavine mono oxygenase (FMOs). The metabolite M1 is metabolized to the metabolite M2 by several CYPs with a limited contribution of CYP3A4 (*in vitro* fm: 29%) and by several FMOs. M2 is not further metabolized.

Elimination

In healthy subjects, after a single oral dose in fasted conditions, fexinidazole was rapidly metabolized to 2 major metabolites, fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2). Only a small fraction (< 3.15%) of the dose administered was recovered in the urine. This fraction was mostly composed of M1 and M2 with only traces of parent drug. The major proportion of M1 and M2 excretion occurred within the first 48 and 120 hours post dose, respectively, into faeces.
In healthy subjects, following the full 10-day treatment regimen, the mean plasma terminal half-life for fexinidazole, M1 and M2 were 14 hours, 15 hours and 23 hours, respectively.

Linearity/non-linearity

In healthy male volunteers, following single oral dosing of fexinidazole over the range 100 to 3600 mg, or repeated oral dosing over the range 1200 to 3600 mg (which covers the therapeutic regimen), under fasted conditions, the systemic exposure of fexinidazole (and subsequently to M1 and M2) was generally less than dose-proportional.

Special populations

Hepatic Impairment
The effect of hepatic impairment has been assessed after the administration of 1200 mg single dose to patients with mild (Child-Pugh A; n=7) or moderate (Child-Pugh B; n=7) hepatic impairment. The AUC of fexinidazole was approximately 1.4-fold higher in patients with hepatic impairment compared to patients with normal hepatic function. Sum of AUCs of active metabolites M1 and M2 was decreased by 18% in

patients with moderate hepatic impairment compared to patients with normal hepatic function. There are no data in patients with severe hepatic impairment (see sections 4.3, 4.4 and 4.2).

Renal Impairment
The effect of renal impairment has not been assessed. In healthy volunteers, < 3.15% of the dose administered was recovered in the urine.

Elderly Patients
No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

Paediatric population
In paediatric patients with g-HAT or r-HAT weighing ≥ 35 kg and receiving the standard dosing regimen, fexinidazole, M1 and M2 exposures (based on concentrations 24 h post-dose on Day 10) were comparable to adult patients exposures, at the end of the maintenance dose (Day 10).
In children with g-HAT or r-HAT weighing [20-35[kg receiving the adjusted dosing regimen, as compared to adult patients receiving the standard dosing regimen, fexinidazole and M1 exposures (based on concentrations 24 h post-dose on Day 10) were 30 to 60 % lower, and M2 exposures were comparable, at the end of the maintenance dose (Day 10, based on concentrations at 24 h post-dose). This had no impact on clinical efficacy (see section 4.4 hospitalisation of patients).

Pharmacokinetic interactions

Effect of other medicinal products on fexinidazole

Given that fexinidazole and the metabolite M1 are metabolized by several CYPs, with a limited contribution of CYP3A4 and by several FMOs, it is predicted that the interaction of CYP3A4 inhibitors or other CYP inhibitors on fexinidazole, M1 and M2 pharmacokinetic exposures should be limited.

It is predicted that the interaction of CYP3A4 inducers should be limited. They could decrease the exposures of fexinidazole, increase the formation of M1 and its clearance. The net effect on M1 pharmacokinetic exposures could be limited and they could also increase the formation of M2 and its exposure. Given that M2 is the major active moiety, it is unlikely that CYP3A4 inducers could modify the efficacy of fexinidazole (see section 4.5).

Effect of fexinidazole on other medicinal products

- *In vitro*: fexinidazole has the potential to inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4/5; M1 has the potential to inhibit CYP2C19; M2 does not inhibit any CYPs. *In vitro*, fexinidazole has the potential to induce CYP3A4 and M1 has the potential to induce CYP3A5; fexinidazole and M1 have the potential to induce CYP1A2; M1 has the potential to induce CYP2B6.
- *In vivo*: a clinical interaction study showed that repeated administration of fexinidazole using the therapeutic loading dose regimen, increased to a limited extent by around 2-fold the exposure of caffeine (CYP1A2 probe) and omeprazole (CYP2C19 probe). Fexinidazole can increase the exposures of medicinal products mainly metabolized by CYP1A2 or CYP2C19.

  In vivo: a clinical interaction study showed that repeated administration of fexinidazole using the therapeutic loading dose regimen decreased the exposure of midazolam (CYP3A4/5 probe). The mean midazolam AUC was decreased by 57%, mean Cmax by 39% and mean $t_{1/2}$ by 33% compared to when midazolam was administered alone. Fexinidazole is considered a moderate CYP3A4/5 inducer (see section 4.5).

  It is predicted that, *in vivo,* fexinidazole could decrease the exposure of medicinal products metabolized by CYP2B6.

  It is predicted that, *in vivo*, the interaction of fexinidazole on CYP2C8, CYP2C9, and CYP2D6 is unlikely.

- *In vitro:* fexinidazole, M1 and/or M2, have the potential to inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K transporters. *In vitro*, fexinidazole, M1 and M2 have no potential to inhibit P-gp, and no significant potential to inhibit BCRP.
- *In vivo*: it is predicted that, *in vivo*, fexinidazole would not increase significantly the exposures of medicinal products which are substrates of OATP1B1 and OATP1B3 transporters. It is predicted that, *in vivo*, fexinidazole could increase the exposures of medicinal products which are significant substrates of OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K transporters. *In vivo*, the interaction of fexinidazole on medicinal products that are substrates of P-gp and/or BCRP is not expected (see section 4.5).

5.3 Preclinical safety data

Safety Pharmacology

No hERG current inhibition was observed with fexinidazole or M1, but an inhibition (32.6%) was noted with M2. There were no related effects on ECG parameters in telemetered conscious dogs at fexinidazole doses of up to 1000 mg/kg. Further, there were no relevant untoward effects on physiological CNS (behaviour and body temperature), cardiovascular or respiratory parameters in preclinical studies.

General and Reproductive Toxicity

Fexinidazole exhibited low toxicity in regulatory preclinical safety studies. In 28-day repeated dose oral toxicology studies, fexinidazole was overall well tolerated in rats and dogs at doses up to 800 mg/kg/day, and effects were essentially limited to decreases in body weight gain and food consumption. The NOAEL was set at 200 mg/kg/day in both species. Systemic exposures (AUCs) at this dose level were nevertheless low as compared to clinical exposure.

No carcinogenicity studies were carried out based on the intended short duration of treatment in humans.

There were no effects on fertility parameters in adult male or female rats after repeated oral doses up to 600 mg/kg/day. Effects observed in embryo-fetal and pre- and post-natal development were regarded as secondary to maternal toxicity, and not as direct developmental effects of fexinidazole. In both the rat and rabbit embryofetal developmental studies, effects on fetal development were observed but only at dose levels which were toxic to the dams (800 and 20 mg/kg, respectively). In the pre- and post-natal development study in the rat, slightly reduced pup weights and delayed sexual maturation occurred at the highest maternal dose of 600 mg/kg/day with no impact on reproductive performance in the F1 generation. In all reproductive toxicity studies, systemic exposures were shown or predicted to be low as compared to clinical exposures.

No preclinical toxicology studies with direct administration of fexinidazole to juvenile animals have been conducted.

Genotoxicity

Fexinidazole and the M2 metabolite were shown to be mutagenic in the Ames test. These results are consistent with the nitroheterocyclic structure of these compounds which can be nitro-reduced by bacterial nitroreductases to form bacterial mutagens, as confirmed by the reduced signal in Ames tests conducted in nitroreductase deficient-strains. In addition, no genotoxic potential was evidenced in a series of *in vitro*, *in vivo* or *ex vivo* tests in mammalian cells. Overall, fexinidazole and its active metabolites are not expected to pose a genotoxic risk to humans.

Phototoxicity

Both the M1 and M2 metabolites of fexinidazole carry a signal for phototoxicity in the 3T3 test at high concentrations, indicating a potential for phototoxicity reactions in subjects treated with fexinidazole and exposed to sunlight or artificial UV-A light. However, the risk is considered to be low, as the tissue distribution study in rats provided no evidence of fexinidazole and/or its metabolites showing a higher

affinity for the skin or the eyes – the two critical tissues for phototoxicity as exposed to light, or binding to melanin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Aluminium/Aluminium foil blisters containing 6, 8, or 12 tablets.
The blisters are packaged into wallets each containing two blisters.
For adults: wallet of 24 tablets (2 blisters of 12 tablets)
For children: wallet of 14 tablets (1 blister of 8 tablets and 1 blister of 6 tablets).

6.6 Special precautions for disposal

No special requirements.
Patients should be advised not to throw away any medicinal products via wastewater or household waste, and to ask their healthcare professional how to dispose of unused medicinal products.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST SCIENTIFIC OPINION / RENEWAL OF THE SCIENTIFIC OPINION

Not applicable

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION
D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Alcami Carolinas Corporation
1519 North 23rd Street
Wilmington
NC 28405
USA

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

- **Periodic safety update reports**

The scientific opinion holder shall submit periodic safety update reports for this product every 3 years until otherwise agreed by the CHMP.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation 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:

- Healthcare staff educational material
- Patient information pack

Healthcare staff educational material:

- The Summary of Product Characteristics
- Guide for healthcare staff (visual aide)

Key messages for the **Guide for healthcare staff**:

- That the healthcare staff should instruct the patients/carers on how Fexinidazole Winthrop should 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 aide)

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 III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - WALLET

1. NAME OF THE MEDICINAL PRODUCT

Fexinidazole Winthrop 600 mg tablets
fexinidazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 600 mg fexinidazole

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

14 tablets
24 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. SCIENTIFIC OPINION NUMBER(S)

Not applicable

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Fexinidazole Winthrop 600 mg tablets
fexinidazole

2. NAME OF THE SCIENTIFIC OPINION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Fexinidazole Winthrop 600 mg tablets
Fexinidazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare staff.
- This medicine has been prescribed for you only. The wallet contains the exact number of tablets you need to treat your disease. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or healthcare staff. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fexinidazole Winthrop is and what it is used for

Fexinidazole Winthrop contains the active substance fexinidazole. It belongs to a group of medicines known as "antiparasitics". It is used in adults and children, of at least 6 years of age and 20 kg in weight, to treat human African trypanosomiasis (also known as "sleeping sickness") caused by the parasite *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiense*.
Fexinidazole should be used in line with official recommendations.

2. What you need to know before you take Fexinidazole Winthrop

Do not take Fexinidazole Winthrop:
- if you are allergic to fexinidazole and/or any nitroimidazole medicines (e.g. metronidazole, tinidazole) or to any of the other ingredients of this medicine (listed in section 6).
- if you have serious liver injury or damage, which can be manifested as yellowing of eyes and mucosa, itching, build-up of fluid in the abdomen, vomiting with blood;
- if you had or have heart problems;
- if any of your relatives had sudden death;
- if you are receiving other medicinal products, except those prescribed by the doctor treating your sleeping sickness.

Warnings and precautions
Talk to your doctor before taking Fexinidazole Winthrop if any of the following apply to you:
- if you had or have mental health conditions;
- if you had or have decreased number of white blood cells (neutropenia);
- if you had or have liver problems;
- if you have a very rare disease named "Cockayne syndrome";
- if you have severe renal problems;
- if you are pregnant or breast-feeding;
- if you have an intolerance to some sugars (lactose).

Depending on the severity of your disease, you may need to be hospitalised to receive your treatment. Your doctor or healthcare staff will explain you how to recognise signs of relapse. If you have any signs of the disease, you need to contact your doctor or healthcare staff without delay. In any case, you will need to have a follow-up visit with your doctor at 12 months after your treatment to check efficacy of the treatment. A follow up visit is needed up to 24 months after your treatment if you have the gambiense type of the disease.

If you suffer from vomiting or diarrhoea or if you have had poor food intake, your doctor may advise you to take foods rich in potassium such as bananas or medicines containing potassium. This is to ensure that you have a sufficient level of potassium in your blood that is needed for the safe use of this medicine.

Some people being treated with fexinidazole can experience mental health problems such as seeing things that are not there, feeling irritated or restless, abnormal behaviour or thinking, feeling anxious, disturbed state of mind, highly excited or happy mood, low mood or feeling depressed, including thoughts of suicide. If you or others around you notice any of these symptoms, contact your doctor or healthcare staff without delay.

Use in children
- For children below 35 kg in weight, the treatment needs be given in hospital.
- Fexinidazole Winthrop should not be given to children below 6 years old and/or less than 20 kg in bodyweight, as the safety and efficacy have not been evaluated in this population.

Other medicines and Fexinidazole Winthrop
Do not use any other medicines during treatment with Fexinidazole Winthrop, unless advised by your doctor. Tell your doctor if you are taking, have recently taken or might take any other medicines, in particular:
- medicines that could change your heart rhythm (example: medicines used to treat irregular heart rhythm, infections, malaria, mental health conditions)
- medicines that could slow your heartbeat (example: beta-blockers)
- disulfiram
- medicinal products containing propylene glycol
- traditional medicines or herbal medicines.

Fexinidazole Winthrop with food and alcohol
- Fexinidazole Winthrop must be taken with food (during or immediately after the main meal of the day) to make sure it is well absorbed into the blood and brain to treat the disease.
- Do not drink alcohol when you take Fexinidazole Winthrop during your treatment and for at least 48 hours after completing your 10-day treatment with this medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Prefer to avoid use of Fexinidazole Winthrop during pregnancy.
Do not breast-feed during Fexinidazole Winthrop treatment unless advised by your doctor.

Driving and using machines
Dizziness, weariness, weakness and sleepiness may occur during the treatment with Fexinidazole Winthrop. It is recommended that you do not drive or use machines if you feel tired or dizzy during the 10 days of treatment with this medicine.

Fexinidazole Winthrop contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Fexinidazole Winthrop.

Fexinidazole Winthrop contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Fexinidazole Winthrop

Always take this medicine exactly as your doctor has told you. This medicine should be taken under the strict supervision of trained health staff. Check with your doctor or healthcare staff if you are not sure.

The recommended daily dose of Fexinidazole Winthrop for adults of at least 35 kg in body weight is 3 tablets (1800 mg) once a day for the first 4 days of treatment, and 2 tablets (1200 mg) once a day for the remaining 6 days (see table below).

Use in children
The recommended daily dose of Fexinidazole Winthrop for children of at least 6 years of age and weighing at least 20 kg but less than 35 kg is 2 tablets (1200 mg) once a day for the first 4 days of treatment, and 1 tablet (600 mg) once a day for the remaining 6 days (see table below).

How to take Fexinidazole Winthrop

Body weight	Number of 600 mg tablets to be taken once daily with food	How many days to take dose
≥ 35 kg Starting dose	3 tablets (1800 mg)	4 days
Maintenance dose	2 tablets (1200 mg)	6 days
≥ 20 and < 35 kg Starting dose	2 tablets (1200 mg)	4 days
Maintenance dose	1 tablet (600 mg)	6 days

Take Fexinidazole Winthrop tablets by mouth.

Take Fexinidazole Winthrop with food (during or immediately after the main meal of the day) once a day for 10 days. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). Do not break or crush the tablets. Try to take your daily dose at about the same time each day. It is important that you take Fexinidazole Winthrop tablets each day for the full course of 10 days.

If you take more Fexinidazole Winthrop than you should
If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Fexinidazole Winthrop
If you accidentally miss a daily dose during the assigned day, just take the next dose at the usual time the following day. Do not take a double dose to make up for a missed dose. Continue to take Fexinidazole Winthrop once a day until all the tablets have been taken. If you miss a second dose, contact your doctor or healthcare staff.

If you vomit after taking Fexinidazole Winthrop
If you vomit after taking Fexinidazole Winthrop, do not take another dose. Take the next dose at the usual time the following day, during or just after the main meal. If you vomit again after any other dose, contact your doctor or healthcare staff.

If you have any further questions on the use of this medicine, ask your doctor, or healthcare staff.

4. Possible side effects

Like all medicines, Fexinidazole Winthrop can cause side effects, although not everybody gets them.

Tell your doctor or healthcare staff if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):
- decreased appetite
- difficulty sleeping
- headache, shaking, dizziness
- vomiting, nausea, indigestion
- feeling weak

Common (may affect up to 1 in 10 people):
- decreased number of red blood cells, decreased number of white blood cells
- decreased blood calcium level, decreased blood sodium level, increased blood potassium level, decreased blood albumin (a protein) level
- seeing things that are not there, feeling irritated or restless, talking excessively, abnormal behaviour, feeling anxious, abnormal thinking
- muscle spasms, restlessness, slow or irregular muscle movements, tingling sensations
- eye pain, light sensitivity
- irregular heartbeat or abnormal heart rhythm
- hot flush
- high blood pressure
- cough
- increase in saliva, dry mouth
- belly pain, inflammation of the stomach, difficulty passing stools
- sweating more
- back pain, neck pain, chest pain
- feeling hot, fever
- change in normal gait

Uncommon (may affect up to 1 in 100 people):
- low blood sugar
- nightmares
- change in personality, sudden abnormal thinking and perception
- disturbed state of mind, highly excited or happy mood, low mood, including having thoughts of suicide
- shaking or spasm, violent muscle contractions with loss of consciousness
- distorted sense of taste
- balance problem
- abnormal voluntary movement, movement problems
- feeling restless with an increase in muscle activity
- itch of the eye, swelling of the eyelid
- ringing in the ears
- increase in heart rate
- difficulty breathing
- hiccups
- pain of the throat
- bloating of the abdomen, abnormal bowel sounds
- diarrhoea
- difficulty swallowing
- belch
- itch of the skin
- pain of the muscle and joints
- pain of the jaw

- muscle spasms
- feeling heavy
- frequent urination at night or during the day, involuntary urination
- chills or feeling cold
- feeling tired
- decrease in blood protein level, calcium or potassium levels

Additional side effects in children
More children reported vomiting within 2 hours of taking Fexinidazole Winthrop than adults.

Reporting of side effects
If you get any side effects, talk to your doctor or healthcare staff. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fexinidazole Winthrop

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the wallet and on the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your healthcare staff how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fexinidazole Winthrop contains
- The active substance is fexinidazole. Each tablet contains 600 mg of fexinidazole.
- The other excipients are lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate.

What Fexinidazole Winthrop looks like and contents of the pack
Fexinidazole Winthrop 600 mg tablets are pale yellow, biconvex, round-shaped and engraved with “4512” on one side.

Fexinidazole Winthrop tablets are supplied:
for children in wallets of 14 tablets (1 aluminium foil blister of 6 tablets and 1 aluminium foil blister of 8 tablets);
for adults in wallets of 24 tablets (2 aluminium foil blisters of 12 tablets).

Scientific Opinion Holder
Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

Manufacturer
Alcami Carolinas Corporation
1519 North 23rd Street
Wilmington
NC 28405

USA

For any information about this medicine, please contact your health care center or the local representative of your National Sleeping Sickness Control Programs (NSSCP).

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu