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.

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* 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
No data are available in patients with hepatic impairment (see section 4.4 and 5.2). Fexinidazole is contraindicated in patients with clinical signs of cirrhosis or jaundice (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 clinical signs of cirrhosis or jaundice (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 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 CSF-WBC > 100 / µL cannot be treated with any other adequate treatment (e.g. NECT).

Risk of relapse

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. 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 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 hypomagnaesemia), 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 pivotal study reported a higher percentage of neuropsychiatric adverse reactions than those treated with nifurtimox eflornithine combination therapy (NECT) (see section 4.8). 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

Fexinidazole is extensively metabolised in the liver (see section 5.2). There is no experience of use in patients with hepatic impairment. The use of fexinidazole is contraindicated in patients with clinical signs of cirrhosis or jaundice.
Reversible elevations of liver transaminases may occur in patients receiving fexinidazole.

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.

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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

- Since the pathways involved in the formation, metabolism and elimination of the active M2 metabolite are unknown and as no drug-drug interaction studies have been performed, it is recommended not to administer any other concomitant medications with fexinidazole. However, 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.

- In addition, 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 drugs known to prolong QT interval or to induce bradycardia or hypokalaemia, 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 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.

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 eflomithine (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 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

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

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, 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	Asthenia	Feeling hot, chest pain,	Chills, fatigue, feeling

administration site conditions		pyrexia, gait disturbance	cold
Investigational		Blood sodium decreased, blood potassium increased	Blood albumin decreased, blood calcium decreased, blood potassium decreased

Description of selected adverse reactions

- Psychiatric related events

Adult patients treated with fexinidazole reported a higher percentage of psychiatric related events (≥1%), including (by decreasing frequency) insomnia, agitation, anxiety, psychotic disorder, abnormal behaviour, depression, logorrhoea, nightmare and personality change than those treated with NECT in pivotal clinical study. 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, 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 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 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: Not yet assigned

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

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 / µLthe 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

*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].

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.

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 metabolised by CYP1A2, CYP2B6, CYP2C19, CYP3A4 and CYP3A5, and also via the human flavin monooxygenase (FMO)-3 enzyme to form the active metabolite, M1, which is then further metabolised to M2. The actual pathways involved in the formation, metabolism and elimination of the active M2 metabolite are currently unknown.

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 postdose, 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 not been assessed.

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
There is no noticeable difference in the pharmacokinetics of paediatric patients weighing ≥ 35 kg, and adult patients.
In children weighing between 28 kg and less than 35 kg, the exposure at the recommended resulted in a lower exposure to fexinidazole and its metabolites (around 20% less) as compared to adults with no impact on clinical efficacy (see section 4.4 hospitalisation of patients).

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 (behavior 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

3 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-aventis groupe
54, rue La Boétie
F-75008 Paris
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.

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-aventis groupe
54, rue La Boétie
F-75008 Paris
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-aventis groupe

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*.
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
- 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 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 relapse, 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 and up to 24 months after your treatment to check efficacy of the treatment.

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.

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 heart beat (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.

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
- 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 and round-shaped.

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-aventis groupe
54, rue La Boétie
F-75008 Paris
France

Manufacturer
sanofi-aventis Kenya
KMA Centre, 6th floor Mara road,
Upperhill, Nairobi
Kenya

sanofi
689, Vasnitex Road
Douala Bonapriso
Cameroon

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