ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acoziborole Winthrop 320 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 320 mg acoziborole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, 9 x 16 mm biconvex oblong uncoated tablets, debossed with “320” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acoziborole Winthrop is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic), including severe second-stage with ≥ 100 White Blood Cell (WBC)/µL with or without trypanosomes in cerebrospinal fluid (CSF), human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* (g-HAT) in adolescents ≥ 12 years old with body weight ≥ 40 kg, and in adults.

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

4.2 Posology and method of administration

Acoziborole Winthrop should be prescribed and administered only by healthcare professionals trained in the management and treatment of HAT.

Posology
Acoziborole Winthrop should be taken once as a single oral dose of 960 mg (three 320 mg tablets).

Vomiting
If vomiting occurs within 15 minutes following the administration of Acoziborole Winthrop, the full dose should be re-administered once only. Three new 320 mg tablets should be taken one at a time.

If vomiting occurs later than 15 minutes following the administration of Acoziborole Winthrop, no re-administration is required.

Paediatric population
The dose for adolescents ≥ 12 years old with body weight ≥ 40 kg is the same as for adults.

The safety and efficacy of acoziborole in children aged < 12 years or with body weight < 40 kg have not been established. No data are available.

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

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

Hepatic impairment
No data are available in patients with hepatic impairment. Use in patients with severe hepatic impairment and/or with clinical signs of jaundice or ascites is not recommended (see section 5.2).

Method of administration
Oral use.
The tablets should be taken without food. Food should not be consumed for at least 2 hours before and 2 hours after administration.

For patients who are unable to swallow whole tablets, the tablets can be crushed until a fine powder is obtained (see section 6.6). The powder should then be immediately administered orally, followed by water to facilitate swallowing.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Acoziborole is contraindicated in patients taking the following medicinal products where retained therapeutic effect is very important to the patient and for which a significant decrease in plasma concentrations is expected together with acoziborole, if compensatory dose adjustments are not possible to retain drug efficacy (see sections 4.4 and 4.5):

- antiretrovirals: atazanavir, darunavir, lopinavir ritonavir, cabotegravir, fostemsavir and lenacapavir
- anti-infective agents: daclatasvir, delamanid, praziquantel, sofosbuvir and voriconazole
- nifedipine

These medicinal products must not be used for 3 months after acoziborole intake.

Acoziborole is contraindicated in patients taking artemether and lumefantrine combination therapy. This combination should not be initiated within one month after acoziborole intake.

Patients with familial short QT syndrome (see sections 4.4 and 5.1).

4.4 Special warnings and precautions for use

Interactions with other medicinal products
Patients treated with chronic concomitant medications should be evaluated by a healthcare provider for interactions with other medicinal products prior to prescribing Acoziborole Winthrop.

Acoziborole is a potent clinical inducer of CYP3A4 and an inducer of other drug-metabolizing enzymes and transporters and may therefore decrease plasma concentrations of a large number of concomitantly used medicinal products. In addition, acoziborole is a strong clinical inhibitor of CYP2D6, and may increase the exposure of concomitant CYP2D6 substrates. Safety or efficacy of concomitant medicinal products may be impacted up to 3 months after acoziborole intake based on its long half-life (12 days) (see sections 4.3 and 4.5).

The SmPC for concomitantly used products should be consulted for the recommendations regarding co-administration with enzyme inducers, particularly strong CYP3A4 inducers, or strong CYP2D6 inhibitors when initiating acoziborole treatment and during 3 months after acoziborole single-dose treatment.

Patient card
The prescriber must explain to the patient the risk related to interactions with other medicinal products. Patients must be provided with the Patient Card and instructed to carry it for 3 months after treatment and show it to all of their healthcare providers during this period.

QT shortening
A shortening of the QT interval has been observed in clinical studies of acoziborole, although no clinical manifestations were observed (see section 5.1). The clinical relevance of QT shortening is unknown. However, due to the potential risk of arrhythmia, acoziborole is contraindicated in patients with familial short QT syndrome (see section 4.3).

Clinicians should use clinical judgment when assessing whether to prescribe acoziborole to patients already treated with a medicinal product known to shorten the QT interval (such as rufinamide, cenobamate, lamotrigine, etc.) or with known risk factors (such as hyperkalaemia or hypercalcemia) (see section 4.3). Caution should also be exercised with regard to prescribing concomitant medication(s) known to shorten the QT interval during the first month after treatment with acoziborole.

Risk of relapse
Patients treated with acoziborole should be made aware of the risk of relapse after therapy and instructed to contact the healthcare provider in case of signs or symptoms of relapse at any time.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Effect of other medicinal products on acoziborole
Based on the distribution and metabolism of acoziborole (see section 5.2), no significant interactions of other medicinal products on acoziborole pharmacokinetics are expected by inhibition or induction of medicinal product metabolizing enzymes or transporters.

Effect of acoziborole on other medicinal products
Acoziborole is a strong clinical inducer of CYP3A4, an inducer of many other inducible drug metabolising enzymes and transporters, and is a strong clinical inhibitor of CYP2D6.

Enzyme and transporter induction
Acoziborole is a potent clinical inducer of CYP3A4 and an inducer of many other drug metabolising enzymes such as CYP2C8, CYP2C9, CYP2C19, CYP2B6, CYP1A2 and uridine 5'-diphospho-glucuronosyltransferase (UGT - glucuronide conjugating enzymes) such as UGT1A1 and UGT1A9. Some transporters might also be induced, e.g. P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Interactions with many medicinal products that are eliminated through metabolism or active transport are expected. The reduction in plasma concentrations can be significant, and lead to reduced clinical effect. There is also a risk of increased formation of active metabolites.

The full induction potential of acoziborole is expected to occur around one week after treatment, lasting for up to one month after dosing, and then gradually decreasing thereafter. Considering the long half-life of acoziborole (12 days, see section 5.2), effects on enzymes may persist for up to 3 months after dosing.

The SmPC for concomitantly used medicinal products should be consulted for the recommendations regarding co-administration with enzyme inducers, particularly strong CYP3A4 inducers.

Medicinal products metabolized by CYP3A4
Acoziborole is a strong inducer of CYP3A4. In healthy participants, co-administration of acoziborole (960 mg single dose) with a single oral dose of midazolam (substrate of CYP3A4) resulted in an 85% and 92% decrease in the C_{max} and AUC_{last} of midazolam, respectively.

For medicinal products that are metabolised by CYP3A4, co-administration could result in a decrease in their exposures. Use of acoziborole is contraindicated in patients taking certain medicines metabolised by CYP34A, as therapeutically effective plasma levels of these medicinal products may not be achieved (see section 4.3). The SmPC for other concomitantly used CYP3A4 substrates (such as fentanyl, quinine) should be consulted for recommendations regarding co-administration with strong inducers. If recommendations for dose adjustment are not available, switching to an alternative concomitant treatment less susceptible to induction should be considered. If co-administration of acoziborole cannot be avoided in a patient already treated with CYP3A4 substrates, monitoring for loss of efficacy (or increase in effect in cases where active metabolites are formed) should be performed, particularly during the first 4 weeks and up to 3 months after acoziborole intake.

Antimalarials
A clinically relevant decrease in drug exposure for artemether and lumefantrine is expected if used together with acoziborole. Co-administration of artemether and lumefantrine combination therapy is contraindicated up to one month after acoziborole administration, when the largest induction effect is expected (see section 4.3). If co-administration of this combination is initiated between one and 3 months after acoziborole administration, there is still a risk for decreased plasma concentration of artemether and lumefantrine potentially resulting in decreased antimalarial efficacy. Monitoring with repeat microscopy should be considered.

Medicinal products metabolized by CYP2C8, CYP2C9, CYP2C19 or UGT-enzymes
Acoziborole induces CYP2C8, CYP2C9, CYP2C19 and UGT1A1 *in vitro* and is expected to induce these enzymes *in vivo*. Caution is advised when acoziborole is used concomitantly with medicinal products which are metabolized by CYP2C8 (such as amodiaquine), CYP2C9 (such as diclofenac, glibenclamide and other sulfonylureas medicinal products), CYP2C19 (such as omeprazole and diazepam) and UGT1A1 (such as dolutegravir and raltegravir), as it could result in a decrease in their exposures. The SmPC for concomitantly used CYP2C/UGT substrates should be consulted for the recommendations regarding co-administration with strong inducers. Adjusting the dose or switching to an alternative concomitant treatment less susceptible to induction should be considered. If co-administration cannot be avoided, patients should be evaluated for possible loss of efficacy (or increase in effect in cases where active metabolites are formed) particularly during the first 4 weeks after acoziborole treatment, when the induction potential of acoziborole is maximal.

Medicinal products metabolized by CYP1A2 and CYP2B6
Acoziborole induces CYP1A2 and CYP2B6 *in vitro.*
Patients taking medicinal products that are substrates of CYP1A2 (such as theophylline) and CYP2B6 (such as efavirenz) should be evaluated for possible loss of efficacy (or increase in effect in cases where active metabolites are formed) particularly during the first 4 weeks after acoziborole treatment, when the induction potential of acoziborole is maximal.

Hormonal contraceptives
Acoziborole may decrease the exposure of systemic hormonal contraceptives, mainly by induction of CYP3A4 and UGT1A1. Therefore, a method of barrier contraception should be used in addition to systemic hormonal contraceptives for 3 months after acoziborole intake (see section 4.6).

Medicinal products that are substrates of P-gp
Acoziborole might induce P-gp potentially leading to decreased exposure of medicinal products that are substrates of P-gp, but no data is available. Medicinal products that are substrates of P-gp (such as

digoxin) should be used with caution when administered concomitantly with acoziborole and monitored for loss of efficacy.
Induction of P-gp by acoziborole at intestinal level may significantly decrease absorption and thereby sofosbuvir plasma concentration, leading to reduced therapeutic effect of sofosbuvir (see section 4.3).

Enzyme and transporter inhibition

Medicinal products metabolized by CYP2D6
Acoziborole is a strong inhibitor of CYP2D6. Co-administration of acoziborole (960 mg single dose) with a single oral dose of dextromethorphan (probe substrate of CYP2D6) to healthy participants resulted in a 13.0- and 35.3-fold increase in the C_{max} and AUC_{last} of dextromethorphan, respectively. The inhibitory effect on CYP2D6 was predicted to persist for 3 months after the administration of acoziborole, in consideration of its long elimination half-life (12. days, see section 5.2).

For medicinal products that are predominantly metabolized by CYP2D6 (such as tramadol and paroxetine), co-administration could result in an increase in their exposure. For medicinal products that are metabolized by CYP2D6 and CYP3A4 (such as haloperidol and risperidone) the net effect of both CYP2D6 inhibition and CYP3A4 induction is unknown. The SmPC for concomitantly used CYP2D6 substrates should be consulted for the recommendations regarding co-administration with strong inhibitors. If co-administration cannot be avoided, dose reduction of such products should be considered at the time of acoziborole treatment and for 3 months afterward and the patient should be monitored for signs of toxicity. If recommendations for dose adjustment are not available, switching to an alternative concomitant treatment less susceptible to CYP2D6 inhibition should be considered. If a treatment with CYP2D6 substrates needs to be initiated within 3 months of treatment with acoziborole, the need to start at the lower end of the dose range of the medicinal product should be considered.

Medicinal products substrates of BCRP transporters
Acoziborole inhibits the BCRP transporters *in vitro* and could increase the exposures of medicinal products which are substrates of BCRP transporters such as sulphasalazine. Caution and monitoring of possible adverse reactions are advised when acoziborole is concomitantly used with such medicinal products as it could result in an increase in their exposure (see section 5.2).

Traditional medicines
It is recommended to avoid the use of traditional or herbal medicines for 3 months after treatment with acoziborole, as the potential interactions are unknown.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in females
Women of childbearing potential should be advised to avoid becoming pregnant and counselled on effective contraception, which should be used for 2 months after acoziborole administration, based on its half-life (see section 5.2).

Women already using hormonal contraception to avoid becoming pregnant should add a barrier contraception method for 3 months after acoziborole treatment, as acoziborole has the potential to reduce hormonal contraceptive efficacy for 3 months after treatment (see section 4.5).

Pregnancy
There is a limited amount of data on the use of acoziborole in pregnant women.

Available pharmacokinetics data in rats have shown that acoziborole crosses the placenta. Animal studies have shown reproductive toxicity (see section 5.3). Placental transfer in humans is unknown.

Acoziborole should not be used during pregnancy unless the clinical condition of the woman with g-HAT requires immediate treatment, and no alternative treatment option is available.

Breastfeeding
There are no data from the use of acoziborole in breastfeeding women. Available pharmacokinetic data in rats have shown that acoziborole is excreted into breast milk (see section 5.3).

There is a risk of accumulation of acoziborole in breastfed children. Therefore, the use of acoziborole is not recommended during breastfeeding.

Fertility
There are no clinical data available on the effects of acoziborole on human fertility. Animal studies have shown reproductive organ toxicity but no effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Acoziborole has minor influence on the ability to drive and use machines. Dizziness and asthenia have been reported following treatment with acoziborole (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions (considered at least possibly related to treatment) were pyrexia (4.8%), asthenia (2.9%), decreased appetite (1.9%), tremor (1.4%) and headache (1.0%). All reported adverse reactions were non serious.

Tabulated list of adverse reactions in g-HAT
Safety data were collected in 208 patients aged 15 years and above in DNDi-OXA-02-HAT (see section 5.1).

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); not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported in treated set of g-HAT patients

System Organ Class	Very Common	Common	Uncommon
Metabolism and nutrition disorders		Decreased appetite	
Nervous system disorders		Tremor Headache	Dyskinesia Dizziness
Gastrointestinal disorders			Abdominal pain Nausea Vomiting
Skin and Subcutaneous Tissue Disorders			Pruritus
General Disorders and Administration Site Conditions		Pyrexia Asthenia	Chills

Investigations	Electrocardiogram QT shortened		

Description of selected adverse reactions

Electrocardiogram QT shortened
A clear association has been seen between administration of acoziborole and shortening of QT interval, which was observed in most of the participants in all studies (see section 5.1).

Paediatric population
There are no safety data from paediatric patients <15 years of age. There are limited clinical data in adolescents from 15 years old.

Other Special Population

Seropositive for g-HAT and non-parasitologically confirmed participants
The safety profile of acoziborole in g-HAT patients was supplemented by supportive safety data obtained from DNDi-OXA-04-HAT, a randomised, double-blind safety and tolerability study of acoziborole in 1 206 g-HAT seropositive non-parasitologically confirmed participants ≥ 15 years old in The Democratic Republic of the Congo and Guinea.

The percentage of participants with adverse reactions was comparable between the 2 arms (acoziborole versus placebo), except for a higher incidence of related headache in the acoziborole treated arm (3.1%) versus the placebo arm (1.7%).

4.9 Overdose

There is no antidote for acoziborole. In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, agents against leishmaniasis and trypanosomiasis.

ATC code: Not yet assigned

Mechanism of action
Acoziborole is a benzoxaborole-6-carboxamide. No specific mechanism of action studies have been performed with acoziborole. Available data suggest that acoziborole binds to Cleavage and Polyadenylation Specificity Factor 3 (CPSF3) in *T. brucei*, inhibiting the maturation of *T. brucei* messenger ribonucleic acid (mRNA). The boron atom in the molecular structure is thought to be essential for the trypanocidal activity, though the precise molecular interactions have not been fully characterized.

Pharmacodynamic effects

In vitro activity
Acoziborole demonstrates potent and selective inhibitory activity against *T. brucei* growth *in vitro*, including in the clinically relevant strains of *T. brucei gambiense* and *T. b. rhodesiense*. Time-kill studies have demonstrated rapid trypanocidal activity.

Cardiac electrophysiology
Shortening of the QT interval, corrected using Fridericia's formula (QTcF), was observed across all clinical studies. The QTcF value was lowest approximately 5 days after administration and returned to baseline values after approximately 1 to 2 months.

Following a single dose of 960 mg in DNDi-OXA-04-HAT (in participants seropositive for *T.b. gambiense*), the observed mean decrease in QTcF from baseline compared to placebo was 11.5 ms (90% CI: -13.7 to -8.11) on day 5. Reduction of QTcF below 340 ms was not observed in a sub-sample of 238 participants of DNDi-OXA-04-HAT. Similar observations were made in DNDi-OXA-02-HAT, with the lowest value being 326 ms.
No cardiac arrhythmias were reported in association with a decreased QTcF interval.

Clinical efficacy and safety

Gambiense HAT

DNDi-OXA-02-HAT
DNDi-OXA-02-HAT was a phase II/III, open-label, prospective, single-arm study in patients ≥ 15 years old with early, intermediate and late-stage parasitologically confirmed HAT due to *T.b. gambiense*, conducted in The Democratic Republic of the Congo (DRC) and Guinea. The primary efficacy endpoint was the treatment success rate in patients with late-stage g-HAT 18 months (M18) after the administration in fasting conditions of a single 960 mg dose of acoziborole. Treatment success was defined as cure (participant alive, no parasites in any body fluids, CSF WBC ≤20 cells/µL on lumbar puncture) or probable cure (missing lumbar puncture at M18 but with CSF WBC ≤20 cells/µL at 12 months (M12) or CSF WBC ≤50 cells/µL at 6 months (M6)).

A total of 208 patients were treated. The median age of the participants was 34.0 years (range 15.0 – 68.0 years), 9 patients were aged between 15 and 17 years old, 117 (56.3%) were male. The mean body weight was 53.2 kg (range 30.0 – 88.0 kg). In early and intermediate-stage patients, and in late-stage patients, the mean (standard deviation) CSF WBC count per microliter was 7.8 (5.3) and 399 (438) respectively.
The treatment success rate at M18 in the modified intention-to-treat (mITT) population (patients with late-stage g-HAT) was 159/167 = 95.2% [95% CI: 91.2%; 97.7%]. A total of 8 patients (4.8%) were considered as treatment failures: 4 patients who died, 3 patients who tested positive for trypanosomes post-baseline and received rescue treatment, and 1 patient who was lost to follow-up.

The treatment success rate at M18 in patients with early- and intermediate-stage g-HAT was 41/41 = 100.0% [95% CI: 94.1%; 100.0%].

Table 2: Efficacy results by Disease severity in the modified intention-to-treat (mITT) population.

	Total (N)	**Success rate at month 18 N(%) [95% CI]***
Early and intermediate stage g-HAT	41	41 (100.0%) [94.1%; 100.0%]
Late-stage g-HAT- Overall	167	159 (95.2%) [91.2%; 97.7%]
Non severe (CSF WBC < 100 cells/µL)	39	38 (97.4%) [88.6%; 99.7%]
Severe (CSF WBC ≥ 100 and < 400 cells/µL)	74	71 (95.9%) [89.6%; 98.8%]

Very severe (CSF WBC ≥ 400 cells/µL)	54	50 (92.6%) [83.3%; 97.4%]

*Jeffreys 95% Confidence Interval

Paediatric population
The efficacy and safety of acoziborole in adolescents aged 12 to < 18 years of age and weighing at least 40 kg have been established based on attainment of systemic drug exposures comparable to adults.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of a single 960 mg dose to fasted patients with g-HAT aged ≥ 15 years, acoziborole was slowly absorbed with a median peak blood concentration observed 48 hours after dosing. The mean concentration remains at a plateau for 96 hours post dose. The mean blood C_{max} was estimated at 11.6 µg/mL (CV = 28.9%) and the mean blood AUC at 5 216 µg.h/mL (CV = 29.6%) (corresponding to 14.3 µg/mL and 6 440 µg.h/mL in plasma, respectively). Acoziborole is a substrate of P-gp transporter, but intestinal Pgp-transport is not expected to play an important role *in vivo*.

Distribution
Acoziborole is highly bound to human plasma proteins *in vitro* (97.8%). Acoziborole has no affinity for blood cells (blood to plasma ratio of 0.81).

The ratio of CSF/blood concentrations in patients with g-HAT aged ≥ 15 years was found to be approximately 1.3% to 1.5% on Day 11 after dosing.

Biotransformation
Acoziborole metabolism is limited *in vivo*, consistent with the low metabolic clearance observed *in vitro*. Acoziborole was the main circulating component in plasma, representing about 95.1% of the total radioactivity in a radiotracer study in six healthy volunteers.

The main pathways of metabolism are oxidative deboronation of acoziborole with further glucuronidation or mono-oxidation, and mono-oxidation of acoziborole. CYP-mediated metabolism is minor. Acoziborole is metabolised by CYP3A4, CYP1A2 and CYP2C8 recombinant human enzymes *in vitro*.

Elimination
Acoziborole had a predominant but slow biliary-faecal elimination with limited metabolism. Radioactivity was predominantly excreted in faeces (74.2% of dose on Day 60) and to a lesser extent in urine (10.9% of dose on Day 16). Renal elimination of unchanged acoziborole is very low (<1%). The mean terminal half-life of acoziborole was 296 hours (12.3 days) in g-HAT patients aged ≥ 15 years.

Linearity/non-linearity
In healthy male volunteers, following single oral dosing of acoziborole over the range 40 to 1 200 mg under fasted conditions, the systemic plasma exposure of acoziborole was generally less than dose-proportional.

Special Populations

Low body weight
In adults weighing < 40 kg, mean C_{max} and AUC values were approximately 17–18% higher compared to those in adults ≥ 40 kg; this difference is not considered clinically relevant.

Paediatric population
Acoziborole PK was studied in 9 paediatric patients ≥15 years of age with g-HAT. Based on a population pharmacokinetic analysis, exposure at the therapeutic dose of 960 mg is comparable between paediatric patients aged ≥12 years with body weight ≥40 kg and adults.

Hepatic Impairment
Acoziborole is primarily eliminated by hepato-biliary clearance and its hepatic metabolism is limited and slow. The pharmacokinetics of acoziborole have not been studied in patients with hepatic impairment and therefore the use of acoziborole in patients with severe hepatic impairment and/or with clinical signs of jaundice or ascites is not recommended (see section 4.2).

Renal Impairment
Renal clearance of unchanged active substance is a minor pathway of elimination for acoziborole. The pharmacokinetics of acoziborole have not been studied in patients with renal impairment.

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

5.3 Preclinical safety data

General Toxicity
Non-clinical toxicity was assessed in 28-day and 13-week repeated dose oral toxicology studies in rats (NOAEL 28d: 5 mg/kg, 13w: 5 mg/kg) and dogs (NOAEL 28d: 5 mg/kg, 13w: 20 mg/kg) in order to achieve similar systemic exposures as those generated by clinical single dose administrations. Overall, the animal-to-human exposure margins for these studies ranged between 0.7-fold to 8.1-fold compared to clinical exposure at the MRHD. The following toxicity of note was observed across species: dilated glands and single cell necrosis in stomach and intestinal segments, spleen (extra-medullary haematopoiesis), pancreas (acinar cell vacuolation), adrenal glands (cortical cell hypertrophy/vacuolation), liver (hepatocellular hypertrophy and single cell necrosis), testes (degeneration of seminiferous tubules). Rat-only toxicity was found in the epididymis (unilateral sperm cell granulomas). Dog-only findings were in the thyroid (follicular epithelial hypertrophy) and kidneys (single cell necrosis). The animal-to-human exposure margins for these findings correspond to ≥ 2.6-fold in rats and ≥ 4.8-fold in dogs.

Genotoxicity
Acoziborole is not genotoxic. No carcinogenicity studies have been conducted.

Developmental & reproductive toxicity
No fertility-related toxicity was observed in rat (FEED study, maximum dose 25 mg/kg, 2.7-fold to 5-fold exposure margins). In embryofoetal development (EFD) toxicity studies, maternal toxicity was observed at 25 mg/kg/day in rat (with no embryofoetal toxicity) and at ≥ 15 mg/kg/day in rabbit. In the latter, resorptions and post-implantation loss was seen at ≥ 5 mg/kg/day (the lowest dose tested) and kidney-ureter malformations at ≥ 15 mg/kg/day. EFD exposure margins were <1-fold (0.7-fold in rats and < 0.1-fold in rabbits). In a rat pre- and postnatal development study (PPND), minimal reduction in pup body weight gain during lactation was observed at 25 mg/kg/day dose level (exposure margin 5-fold) without any impact on the post-weaning development including the reproductive performance of F1 generation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Magnesium stearate
Microcrystalline cellulose
Povidone

Sodium starch glycolate type A.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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

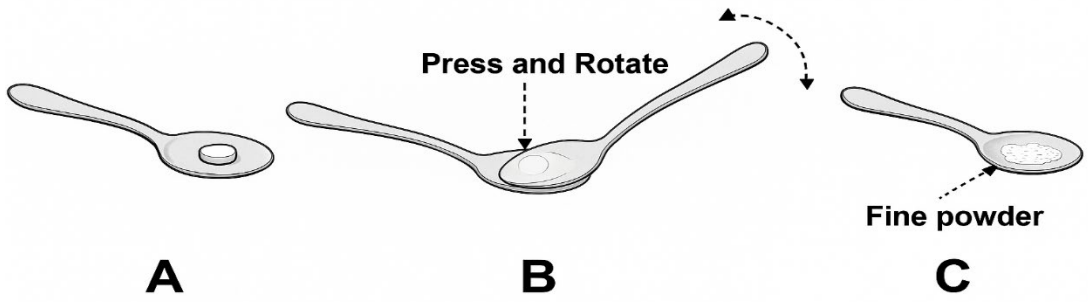
Polyamide/aluminium/PVC/PVDC/aluminium blister pack.
Pack size of 3 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Crushing of tablets between spoons
The tablets can be crushed, one at a time, between two spoons (both spoons facing the same way).
Refer to Figure 1 below:

Figure 1 – Crushing Tablets Between Two Spoons



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 https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Patheon France
40 Boulevard De Champaret,
38300 Bourgoin Jallieu
France

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the scientific opinion holder (SOH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The scientific opinion holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion 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 Acoziborole Winthrop in target countries, the scientific opinion holder must agree with the National Competent Authority the modalities part of the National Sleeping Sickness Control Program (NSSCP) including Risk Minimization Measure (RMM) control tools, and the educational programme.
Risk minimization tools are aimed at ensuring that patients are informed on the safe use of the medicine, that they are supervised by trained health care staff (healthcare professional [HCP] qualification), and at ensuring that the product is shipped according to the needs in endemic countries and distributed in NSSCP selected health care centers (traceability system) where HCP have been trained for safe use and administration of Acoziborole only to Human African Trypanosomiasis (HAT)-diagnosed patients.
The educational programme is aimed at ensuring that patients and other healthcare professionals (HCPs or medical referents involved in patient's care for other conditions) are informed on the

potential effect of Acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction), during the three month period following acoziborole administration.

The scientific opinion holder shall ensure that in countries where Acoziborole Winthrop is distributed, all HCPs, medical referents and "patients/caregivers exposed/receiving Acoziborole Winthrop" have access to/are provided with the following educational/safety advice tool:

Healthcare staff educational material:

- The Summary of Product Characteristics
- The Patient Card

Key messages of the Patient Card:

The card includes:

- Treatment date, drug-drug interaction (DDI) end date, treatment center and patient contact details.
- Acoziborole indication.
- Information about DDI, reminder of contraindication and caution with some drugs mainly metabolized by CYP2D6 or CYP3A4, and to not use traditional medicines, for 3 months post-acoziborole treatment.
- Reminder for the Human African Trypanosomiasis (HAT) HCP to alert the patient about DDI and to give the Patient Card to the patient.
- Instructions for the patients to discuss DDI and/or to show the card to other HCPs or medical referents not trained in *Gambiense* Human African Trypanosomiasis (g-HAT) and to dispose of the Patient Card 3 months after Acoziborole treatment (through visuals).
- National or World Health Organization (WHO) Pharmacovigilance system contact details to report adverse events (AEs).

The patient information pack:

- A Patient Leaflet
- A Patient Card – see description above

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS):	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Acoziborole Winthrop 320 mg tablets
acoziborole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 320 mg acoziborole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
3 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<, DONATION AND PRODUCT CODES>

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

Acoziborole Winthrop 320 mg tablets
acoziborole

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

Acoziborole Winthrop 320 mg tablets
acoziborole

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
- 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 Acoziborole Winthrop is and what it is used for

Acoziborole Winthrop contains the active substance acoziborole. It belongs to a group of medicines known as "antiparasitics". It is used in adolescents 12 years and older and with body weight of at least 40 kg, and in adults to treat human African trypanosomiasis (also known as "sleeping sickness") caused by the parasite *Trypanosoma brucei gambiense*.

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

Do not take Acoziborole Winthrop:
- if you are allergic to acoziborole or any of the other ingredients of this medicine (listed in section 6)
- if you are taking the following medicines (see section “Other medicines and Acoziborole Winthrop”):
  - artemether and lumefantrine combination (antimalarial medicine)
  - antiretroviral medicines (for HIV/AIDS): atazanavir, darunavir, lopinavir, ritonavir, cabotegravir, fostemsavir and lenacapavir
  - daclatasvir and sofosbuvir (antiviral for the treatment of hepatitis C)
  - delamanid (anti-tuberculosis medicine)
  - praziquantel (antiparasitic medicine)
  - nifedipine (medicine to treat heart conditions or to lower blood pressure)
  - voriconazole (antifungal medicine)
- if you have a heart beat problem called ‘familial short QT syndrome’

Warnings and precautions
Talk to your doctor before taking Acoziborole Winthrop if any of the following apply to you:
- if you or anyone in your family have a history of heart beat problems or history of fainting (syncope) or sudden death.
- if you have or have had liver problems. If your liver disease is severe the doctor may decide Acoziborole Winthrop is not recommended for you as the safety and efficacy have not been evaluated in patients with liver disease.

Your healthcare professionals will explain to you how to recognise signs of relapse of sleeping sickness. If you have any signs of the disease, you need to contact your healthcare professionals without delay.

Children and adolescents
Acoziborole Winthrop should not be given to children under 12 years of age or with body weight less than 40 kg, as the safety and efficacy have not been evaluated in these populations.

Other medicines and Acoziborole Winthrop

Tell your doctor if you are taking, have recently taken or might take any other medicines.
Other medicines can be affected by Acoziborole Winthrop for up to 3 months after you take it. Your healthcare provider will explain the details to you and give you a card to remind you about it. Carry this card with you and show it to any healthcare providers you consult for 3 months after your treatment.

Do not take Acoziborole Winthrop if you are taking the following medicines:
- artemether and lumefantrine combination (antimalarial medicine)
- antiretroviral medicines (for HIV/AIDS): atazanavir, darunavir, lopinavir, ritonavir cabotegravir, fostemsavir and lenacapavir
- daclatasvir and sofosbuvir (antiviral for the treatment of hepatitis C)
- delamanid (anti-tuberculosis medicine)
- praziquantel (antiparasitic medicine)
- nifedipine (medicine to treat heart conditions or to lower blood pressure)
- voriconazole (antifungal medicine)

The following medicines can be affected by Acoziborole Winthrop for up to 3 months after taking Acoziborole Winthrop. Your doctor may need to change the dose of the following medicines or give you other medicine:
- Amodiaquine and quinine (medicines for malaria)
- Diazepam (medicine for anxiety and epilepsy)
- Diclofenac (medicine for pain and fever)
- Digoxin (medicine for cardiac disorder)
- Dolutegravir, efavirenz and raltegravir (medicines for HIV/AIDS)
- Fentanyl (strong painkiller)
- Glibenclamide and sulfonylureas (medicine for diabetes)
- Hormonal contraceptive, such as injection, implant or pill (see section Contraception in women)
- Omeprazole (medicine to reduce stomach acid)
- Theofylline (medicine for asthma)
- Paroxetine (medicine for mental health conditions)
- Sulphasalazine (medicine for inflammatory bowel disease)
- Tramadol (strong painkiller)
- Haloperidol and risperidone (medicines for mental health conditions)

It is not recommended to use traditional or herbal medicines for 3 months after the treatment with Acoziborole Winthrop, as it is not known how these can affect or be affected by Acoziborole Winthrop.

Pregnancy, breast-feeding and contraception

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should not take this medicine during pregnancy unless your

healthcare professional states it is clearly necessary. There might be a risk to your unborn baby. Your healthcare professional will discuss that with you.

Breast-feeding
If you are breastfeeding or are planning to breast-feed, ask your doctor for advice before taking this medicine. Acoziborole may pass into breast milk. It is not recommended to take acoziborole if you are breast feeding.

Contraception in women
You should avoid becoming pregnant for 2 months after treatment with Acoziborole Winthrop. This is how long acoziborole remains in your body.
If you are able to get pregnant you should use an effective method of contraception for 2 months after taking acoziborole.
If you are already using hormonal contraceptives (such as injection, implant or pill), you should add a barrier method for 3 months. Hormonal contraception may be less effective for 3 months after acoziborole intake.
Your healthcare professional will advise you further.

Driving and using machines
Dizziness, fatigue, blurred vision may occur after treatment with Acoziborole Winthrop (see section 4). It is recommended that you do not drive or use machines if you experience these side effects.

Acoziborole Winthrop contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

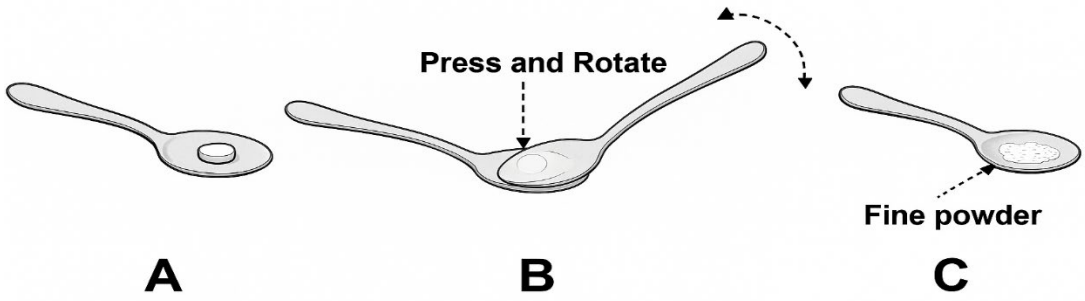
3. How to take Acoziborole Winthrop

This medicine should be taken under the strict supervision of trained health staff.
The recommended dose is 3 tablets (960 mg) in adolescents 12 years and older and with a body weight of at least 40 kg and in adults. All tablets are taken one by one, at the same time without food. You should not take food from 2 hours before until 2 hours after taking this medicine.
Take Acoziborole Winthrop tablets by mouth with water.

If you vomit within 15 minutes after intake, you should take 3 new tablets under the supervision of health staff.

If you cannot swallow whole tablets, the tablets can be crushed, one tablet at a time between two spoons (both spoons facing the same way) until a fine powder is obtained. The powder is to be swallowed immediately, directly from the spoon used for crushing, followed by water to facilitate swallowing. Refer to Figure 1 below:

Figure 1 – Crushing Tablets Between Two Spoons



4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Tell your healthcare provider if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):
- Changes on the electrocardiogram (ECG)

Common (may affect up to 1 in 10 people):
- Decreased appetite
- Shaking (tremor)
- Fever (pyrexia)
- Headache
- Weakness (asthenia)

Uncommon (may affect up to 1 in 100 people):
- Difficulty controlling movement (dyskinesia)
- Dizziness
- Abdominal pain
- Nausea
- Vomiting
- Itching (pruritus)
- Chills

Reporting of side effects
If you get any side effects, talk to your healthcare provider. 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 Acoziborole 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 carton 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 to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your healthcare provider 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 Acoziborole Winthrop contains
- The active substance is acoziborole. Each tablet contains 320 mg of acoziborole.
- The other ingredients are: calcium hydrogen phosphate dihydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate type A (see section 2 “Acoziborole Winthrop contains sodium”).

What Acoziborole Winthrop looks like and contents of the pack
Acoziborole Winthrop 320 mg tablets are white, 9 x 16 mm biconvex oblong tablets, engraved with "320" on one side.

Acoziborole Winthrop tablets are supplied as 3 tablets in an aluminium foil blister pack.

Scientific Opinion Holder
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82 avenue Raspail
94250 Gentilly
France

Manufacturer
Patheon France
40 Boulevard De Champaret,
38300 Bourgoin Jallieu
France

This leaflet was last revised in month

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