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I.6 Fexinidazole: Trypanosoma brucei rhodesiense (r-HAT)

MSF strongly supports the new indication for fexinidazole in both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc), for treatment of human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense* (r-HAT) in adult and children ≥ 6 years old and weighing ≥ 20 kg. Fexinidazole is already included in both EML and EMLc for the treatment of first stage and second stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* (g-HAT).

Human African trypanosomiasis, commonly known as sleeping sickness, is a life-threatening parasitic infection transmitted through the bite of infected tsetse flies, endemic to sub-Saharan Africa. The disease advances through 2 stages: first stage (haemo-lymphatic) and second stage (meningo-encephalitic).
Trypanosoma brucei gambiense (g-HAT) is responsible for around 92 % of reported cases and is endemic across western and central Africa. It causes a chronic infection where individuals may remain asymptomatic for months to years before developing symptoms and progresses to neurological impairment with sleep disturbances, cognitive impairment, and behavioral changes if untreated, leading to coma and death within 2–3 years.
Trypanosoma brucei rhodesiense (r-HAT), "the neglected among the neglected diseases", is responsible of around 8 % of reported cases and is endemic in 13 countries across eastern and southern Africa (but cases have been declared in 7 countries during the last 15 years). It causes an acute, rapidly progressing illness as the first symptoms appear within 1 to 3 weeks and progresses, from first to second stage within 3 to 8 weeks, to multi-organ failure and central nervous system severe damages, often being fatal (cardiac failure and arrest) within 4 to 6 months if untreated.

Currently, the medicines already included in the EML and EMLc for the treatment of human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* are injectable suramin sodium for the treatment of 1st stage r-HAT, and injectable melarsoprol for the treatment of 2nd stage r-HAT.
Suramin and melarsoprol were used for the treatment of human African trypanosomiasis since their discovery, respectively in 1920 and 1949. Suramin is associated with several side effects (nephrotoxicity, haemolytic anaemia, peripheral neuropathy, bone marrow toxicity). Melarsoprol (organoarsenic compound) intravenous injection is painful, often causes thrombophlebitis and vein fibrosis and is frequently associated with severe complications as post-treatment reactive encephalopathy occurs in up to 10% of treated patients.

In 2019, WHO issued interim guidelines for treatment of human African trypanosomiasis due to *Trypanosoma brucei gambiense* (1) including oral fexinidazole in first stage and non-severe second stage, with some limitations of age and body weight and following some important specific rules to ensure efficacy. In first-stage, intramuscular pentamidine can be also used, and in second-stage nifurtimox–eflornithine combination therapy.
In 2019, the Expert Committee on the Selection and Use of Essential Medicines recommended the addition of fexinidazole to the EML and EMLc as an oral treatment for both the first stage and second stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* in adults and children ≥ 6 years old and weighing ≥ 20 kg.

In December 2023, following an application by Sanofi and clinical trials in Malawi and Uganda led by the non-profit medical research organization Drugs for Neglected Diseases initiative (DNDi), the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive scientific opinion of fexinidazole as the first oral treatment of acute form of sleeping sickness, for the treatment of both first-stage and second-stage *Trypanosoma brucei rhodesiense* infection, in adults and children ≥ 6 years old and weighing ≥ 20 kg. This positive opinion followed the CHMP first adopted positive opinion in 2018 of fexinidazole as the first all-oral treatment, in adults and children ≥ 6 years old and weighing ≥ 20 kg, of both first-stage and second-stage of the more common *Trypanosoma brucei gambiense* form of sleeping sickness.

In June 2024, WHO "Guidelines for the treatment of human African trypanosomiasis" stated that the first-choice treatment is determined first by the patient's age and body weight, and by the CSF examination (lumbar puncture) only for children < 6 years old or body weight < 20 kg and recommended fexinidazole as the first-choice treatment in r-HAT patients aged ≥ 6 years and body weight ≥ 20 kg. Suramin is the first-choice treatment in patients aged < 6 years or body weight < 20 kg presenting with ≤ 5 white blood cells (WBC)/µL in CSF and no trypanosomes in CSF. Melarsoprol is the first-choice treatment in patients aged < 6 years or body weight < 20 kg presenting with > 5 WBC/µL or trypanosomes in CSF (2).

The new indication proposed by Sanofi Winthrop to be add for fexinidazole in the 2025 EML is the treatment of both the first stage and second stage of human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* in adults and children ≥ 6 years old and weighing ≥ 20 kg.

MSF would like to draw the attention of the Expert Committee to the following points:

- In 2024, in its most recent guidelines, WHO recommended fexinidazole to replace suramin and melarsoprol as the first-line treatment in r-HAT patients aged ≥ 6 years and body weight ≥ 20 kg. Because the efficacy evidence for fexinidazole in rhodesiense HAT is still limited, appropriate follow-up to detect a relapse early is essential.

- Fexinidazole offers the important advantage of oral administration over suramin and melarsoprol which require intravenous or intramuscular injections and which carry significant toxicity risk (including melarsoprol's 8% treatment-related fatality rate). Fexinidazole is indicated as a 10-day oral treatment and must be taken once daily with food during or immediately after the main meal of the day, with a loading dose over four days and a lower maintenance dose over the following six days.

- Lumbar puncture for cerebrospinal fluid examination is no longer needed in most cases. It is only needed to make the choice of treatment for patients that fall outside the fexinidazole indication: aged < 6 years or body weight < 20 kg or who have contraindications for the use of fexinidazole.

- On 30 January 2025, WHO delivered fexinidazole to the health authorities of Malawi and Zimbabwe, supporting by training programs for health care workers and active pharmacovigilance programs during the initial years (3).

- Fexinidazole has already been registered in the Democratic Republic of the Congo and Uganda as a treatment for *Trypanosoma brucei gambiense* and is recommended for use in a

further 10 African countries (Angola, Burkina Faso, Central African Republic, Chad, Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Guinea, and South Sudan).

- Fexinidazole is donated to WHO by the manufacturer Sanofi to treat all patients worldwide, while its stock management and shipment are undertaken by Médecins sans Frontières-Logistique according to the agreement signed with WHO. Transport costs to countries are paid by the manufacturer through its partnership with WHO. Fexinidazole is distributed free of charge in the *Trypanosoma brucei rhodesiense* endemic countries through the WHO Neglected Tropical Diseases department to National Sleeping Sickness Control Programs, then to the treatment centers.

- In October 2024, to support national and global efforts to increase access to and the affordability of care and treatment of neglected tropical diseases, WHO invited manufacturers of medicinal products for treatment of neglected tropical diseases to submit an Expression of Interest for product evaluation to the WHO Prequalification Unit including fexinidazole 600 mg tablet.

MSF has been using fexinidazole in its programs for treatment of both stages of human African trypanosomiasis due to *Trypanosoma brucei gambiense* since 2018.

Considering all these elements, MSF urges the 25th Expert Committee on the Selection and Use of Essential Medicines to add to fexinidazole the indication for treatment of human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* in adult and children ≥ 6 years old and weighing ≥ 20 kg, in both the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children.

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