Fexinidazole

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EMLc | ATC codes: P01CA03

Indication	Rhodesiense trypanosomiasis ICD11 code: 1F51.1
INN	Fexinidazole
Medicine type	Chemical agent
List type	Core
Additional notes	For the treatment of 1st and 2nd stage of human African trypanosomiasis due to Trypanosoma brucei gambinense and Trypanosoma brucei rhodesiense infection
Formulations	**Oral > Solid > tablet:** 600 mg
EML status history	First added in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Fexinidazole
DrugBank	Fexinidazole

Expert Committee recommendation

The Expert Committee acknowledged the public health relevance of human African trypanosomiasis due to Trypanosoma brucei rhodesiense as a rare, but serious neglected tropical disease, that is usually fatal if untreated. The Committee noted the evidence for fexinidazole comes from a single trial in a small number of patients, which demonstrated the effectiveness of the medicine in reducing fatality rates to within acceptable limits, albeit with limited follow-up. The Committee also noted that no new safety signals beyond those already known for fexinidazole were identified. The Committee acknowledged support for the inclusion of fexinidazole on the EML and EMLc from the WHO technical department and that fexinidazole is recommended in current WHO guidelines for the treatment of African trypanosomiasis due to T. b rhodesiense infection. The Committee considered that as an orally administered treatment, the use of fexinidazole may offer both patient and health-system advantages compared with parenteral administration of other medicines used in the treatment African trypanosomiasis due to T. b. rhodesiense (e.g. suramin, melarsoprol). The Committee also noted that fexinidazole would be provided free of charge through the WHO Department of Control of Neglected Tropical Diseases to national sleeping sickness control programmes and treatment centres. Based on these considerations, the Expert Committee therefore recommended the inclusion of fexinidazole on the EML and EMLc for the new indication of treatment of first- and second-stage African trypanosomiasis due to T. b. rhodesiense infection.

Background

Fexinidazole has not previously been evaluated for inclusion on the Model Lists for the treatment of human African trypanosomiasis due to Trypanosoma brucei rhodesiense (r-HAT). Fexinidazole was included in 2019 for treatment of first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis due to Trypanosoma brucei gambiense (g-HAT) in adults and children. The Model Lists currently include suramin sodium and melarsoprol for treatment of first- and second-stage r-HAT, respectively.

Public health relevance

Human African trypanosomiasis, or sleeping sickness, is one of the most neglected tropical diseases. Without diagnosis and treatment, it is usually fatal as the parasites multiply in the body, cross the blood–brain barrier and invade the central nervous system at the late stage of the disease. Human African trypanosomiasis takes two forms, depending on the parasite involved: Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense. r-HAT is a rare disease that contributes to a small proportion of cases of human African trypanosomiasis (about 1.5% (110/7201) in 2012 and about 3.4% (24/699) in 2023) (1, 2). r-HAT is an acute and aggressive form of human African trypanosomiasis, as the first symptoms appear within 1 to 3 weeks and the progression from the first to second stage occurs within 3 to 8 weeks. If left untreated, r-HAT patients generally suffer from central nervous system impairment and usually die within 4 to 6 months from cardiac failure and cardiac arrest (3, 4). r-HAT and g-HAT differ in most of their characteristics (3, 5). r-HAT is a zoonotic disease with humans being accidental hosts, while humans are the primary hosts for g-HAT. T. b. rhodesiense parasites are transmitted by tsetse flies of the Glossina morsitans species. This species lives in drier and more open areas of woodlands and savannahs than the tsetse flies of the Glossina palpalis group that live in riverine and forest areas and which transmit g-HAT parasites (6). Wildlife and domestic animals (mainly cattle) are the animal reservoirs of T. b. rhodesiense parasites (7). Encroachment into wildlife areas and the increasing density of livestock and humans are key factors that sustain trypanosome transmission (8). In contrast to g-HAT diagnosis, no serological field diagnostic tests are available for r-HAT, which depends on the microscopic detection of parasites mainly in blood and cerebrospinal fluid from suspected clinical cases. Both T. b. rhodesiense and T. b. gambiense trypanosomes can only be distinguished from each other by molecular biological tests which are not available in most African health facilities with HAT expertise (9). Trypanosome distinction therefore relies on the specific geographical distribution of each subspecies: T. b. rhodesiense in east and south-eastern Africa (e.g. Ethiopia, Kenya, Malawi, southern Uganda, United Republic of Tanzania, Zambia and Zimbabwe) and T. b. gambiense in west and central Africa (e.g. Angola, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Guinea, South Sudan and north-eastern Uganda) (1–3).

Benefits

Evidence for the efficacy of fexinidazole in patients with r-HAT is based on data from one (yet to be published) single-arm non-randomized trial (DNDi-FEX-07-HAT) conducted in 45 adult and paediatric (aged ≥ 6 years and weighing ≥ 20 kg) patients with stage 2 (n = 35) and stage 1 (n = 10) r-HAT in Malawi and Uganda. The primary objective of the study was to demonstrate that the fatality rate at end of hospitalization was lower than a predetermined unacceptable fatality rate of 8.5%. The primary endpoint was the fatality rate at end of hospitalization (day 12 to day 18), defined as the rate of fatalities possibly related to r HAT or to fexinidazole (according to the data safety monitoring board) in patients with stage 2 r-HAT. The population analysed for the primary endpoint was 34 stage-2 r-HAT patients who could be evaluated. One patient was excluded due to death on day 8 for a reason considered unrelated to r-HAT or treatment. The fatality rate at end of hospitalization was 0.0% (90% confidence interval (CI) 0.00% to 8.43%). Analyses in the modified intention-to-treat population (n = 35) and the total population (n = 44) reported fatality rates of 0.00% (90% CI 0.00% to 8.20%) and 0.0% (90% CI 0.00% to 6.58%), respectively. As the upper limit of the 90% CI was less than 8.5%, thereby excluding the threshold of unacceptable fatality rate, the null hypothesis was rejected. Secondary efficacy endpoints were related to failure rates in r-HAT patients who could be evaluated and were assessed at end of hospitalization and at 12 months (end of study) in stage 2, stage 1 and the total evaluable population. Failure was assessed by the presence of trypanosomes in blood or cerebrospinal fluid at the end of treatment, death related to r-HAT or study

treatment at end of hospitalization, or absence of clinical improvement leading to the use of rescue medication. Predetermined unacceptable failure rates were 9% at the end of hospitalization and 12% at 12 months. At the end of hospitalization, the failure rate in the evaluable stage 2 r-HAT patients was 0.0% (90% CI 0.00% to 8.43%). Results in the total evaluable population were similar. The sample size of stage 1 r-HAT patients (n = 10) was too small to be compared to the unacceptable failure rate. At 12 months, the failure rate in the stage 2 r-HAT patients who could be evaluated was 2.94% (90% CI 0.15% to 13.21%). In the overall population, the failure rate was 2.27% (90% CI 0.12% to 10.34%). No failures were reported in evaluable patients with stage 1 r-HAT.

Harms

No new safety signals were reported for r-HAT patients and safety findings were generally consistent with the safety profile of fexinidazole established from previous studies in healthy subjects and patients with g-HAT. A total of 45 patients with r-HAT were exposed to fexinidazole in the above-mentioned trial. During hospitalization, 40 treatment-emergent adverse events were reported in 22/45 (49%) r HAT patients. Seven treatment-emergent adverse events were reported in five patients and were considered to be mild-to-moderate intensity and not serious. These events included electrocardiogram U-wave abnormalities, QT prolongation (QTcF < 500 ms), increased blood pressure, gastritis and vomiting. A total of 32 non-serious adverse events considered unrelated to treatment occurred in 18 patients. One serious adverse event of acute renal injury was reported in one patient. It was considered unrelated to the treatment or the disease, led to permanent treatment discontinuation after seven doses and to the patient's death on day 8. During the follow-up period (starting from the month-1 visit), only adverse events considered possibly related to fexinidazole and all serious adverse events were reported. Two serious adverse events considered unrelated to the treatment (or disease) were reported in two patients. Overall, no adverse events of special interest, defined as neuropsychiatric signs and symptoms (excluding headaches and insomnia) requiring specialized therapeutic intervention, were reported.

Cost / cost effectiveness

Medicines for treatment of HAT are provided free of charge to WHO through a public–private partnership between WHO/Sanofi (eflornithine, fexinidazole, melarsoprol and pentamidine) and WHO/Bayer AG (nifurtimox and suramin). Sanofi signed an agreement with WHO in 2001, under which medicines for HAT are donated to WHO, to be used exclusively for its treatment. Requests for supplies are made to WHO by governments of disease-endemic countries and organizations working in association with these governments. Stock management and shipment of the medicines are undertaken by Médecins sans Frontières-Logistique according to the singed agreement. Transport costs are paid by Sanofi. In the same way as is currently done for fexinidazole for g-HAT, fexinidazole will be distributed free of charge in countries endemic for r-HAT through the WHO Department of Control of Neglected Tropical Diseases to national sleeping sickness control programmes and from there to the treatment centres. The product will not be available through pharmacies or out of the predefined distribution system. No return on investment is expected.

WHO guidelines

The 2024 WHO guidelines for the treatment of HAT (10) include the following conditional recommendations for the use of fexinidazole in the treatment of r-HAT. • In patients aged ≥ 6 years and with body weight ≥ 20 kg with first-stage r-HAT, use fexinidazole over suramin (very low-certainty evidence) • In patients aged ≥ 6 years and with body weight ≥ 20 kg with second-stage r-HAT, use fexinidazole over melarsoprol (very-low-certainty evidence). Melarsoprol may be preferred in patients who: are unable to swallow; have a contraindication to fexinidazole; have persistent vomiting; or have questionable oral absorption. • In pregnant women, given the rapid clinical evolution of r-HAT, treatment cannot usually be delayed. Clearly explain the benefits and risks to the patient and their relatives. Fexinidazole and pentamidine are preferred. Suramin and melarsoprol may become necessary as rescue treatment (very-low-certainty evidence). • For fexinidazole to be absorbed at therapeutic levels, it must be taken in a fed condition (i.e. with or after food). As a condition of prescribing, the prescriber must have confidence in the availability of food for the patient, which will be eaten immediately before administration of the medicine each day (low-certainty evidence). • Each intake of fexinidazole must be supervised by a trained health staff who

must ensure that the patient is in a fed condition (directly observed treatment) (very-low-certainty evidence). • Hospitalization is preferred and should be mandatory in patients presenting with psychiatric disorders, a history of alcohol use disorder, body weight lower than 35 kg, and vomiting following fexinidazole administration (very-low-certainty evidence).

Availability

Fexinidazole is currently approved in three countries worldwide: Democratic Republic of the Congo, Uganda and the United States of America. On 14 December 2023, Sanofi received a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use on the extension of indications for fexinidazole to include treatment of both first- and second-stage r-HAT. The extension of indications has also been approved in the Democratic Republic of the Congo and a registration application was submitted in May 2024 in Uganda. Specific regulatory and distribution procedures for HAT therapies are in place. The current HAT medicines are not registered in all endemic countries but are registered in at least one Stringent Regulatory Authority. The stand-alone distribution system for all HAT medicines including fexinidazole is managed by WHO. The system allows import and distribution in other endemic countries through a letter of interest from national authorities to WHO, stating the inclusion of fexinidazole in the national HAT treatment policy. The same distribution system will apply to fexinidazole for r-HAT in the corresponding endemic countries.

Other considerations

HAT is categorized as first-stage or second-stage for the purpose of guiding therapeutic choices via cerebrospinal fluid examination: • first-stage (haemo-lymphatic stage): ≤ 5 white blood cells/µL AND no trypanosomes in cerebrospinal fluid • second-stage (meningo-encephalitic stage): > 5 white blood cells/µL OR trypanosomes in cerebrospinal fluid. Because fexinidazole is effective for both stages of HAT, cerebrospinal fluid examination is needed only to guide the choice of treatment for patients who are not captured by the approved indications for fexinidazole (i.e. aged < 6 years or body weight < 20 kg, or who have contraindications to the use of the medicines). Diagnostic tests for basic cerebrospinal fluid profile are included on the WHO Model List of Essential In Vitro Diagnostics (11).

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