Fexinidazole

Statut de médicament essentiel

Section: 6. Anti-infective medicines > 6.5. Antiprotozoal medicines > 6.5.5. Antitrypanosomal medicines > 6.5.5.1. African trypanosomiasis > 6.5.5.1.2. Medicines for the treatment of 2nd stage African trypanosomiasis

EMLc | Codes ATC: P01CA03

Indication	African trypanosomiasis Code ICD11: 1F51
INN	Fexinidazole
Type de médicament	Chemical agent
Type de liste	Liste de base (EML) (EMLc)
Additional notes	For the treatment of 1st and 2nd stage of human African trypanosomiasis due to Trypanosoma brucei gambinense infection
Formulations	Oral > Solid: 600 mg
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Fexinidazole
DrugBank	Fexinidazole

Recommandation du comité d'experts

The Expert Committee recommended the listing of fexinidazole on the core list of the EML and EMLc for treatment of human African trypanosomiasis due to Trypanosoma brucei gambiense infection. The Committee noted that fexinidazole was demonstrated in clinical trials to have success rates within acceptable margins compared to NECT, and acceptable safety. The Committee acknowledged that as an orally administered treatment, use of fexinidazole may offer both patient and health system advantages compared to parenteral administration of other medicines for this disease. The Committee noted that fexinidazole would be provided free of charge through the WHO NTD department to national sleeping sickness control programmes and treatment centres, and could contribute to the goal of disease eradication, particularly in areas where access to health facilities is limited.

Contexte

The application requested listing of fexinidazole on the core list of the EML and EMLc for treatment of human African trypanosomiasis due to Trypanosoma brucei gambiense infection. Fexinidazole had not previously been considered for inclusion on the Model Lists. The Model Lists currently include pentamidine and suramin sodium for treatment of 1st stage African trypanosomiasis and eflornithine, melarsoprol and nifurtimox for treatment of 2nd stage African trypanosomiasis (1).

Pertinence pour la santé publique

Human African trypanosomiasis (HAT), or sleeping sickness, is one of the most neglected tropical diseases (NTDs). Without

diagnosis and treatment, HAT 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 HAT and Trypanosoma brucei rhodesiense HAT. T. b. rhodesiense causes an acute, rapidly progressive and fatal disease and is present in 3% of HAT cases. T. b. gambiense is responsible for 97% of HAT cases (2) and evolves to a fatal outcome between two and three years after infection (3). As of October 2012, 7106 annual cases of T. b. gambiense HAT had been reported worldwide. With the increased efforts of control programmes and availability of combination therapy with eflornithine and nifurtimox (NECT) therapy, only 1420 gambiense HAT cases worldwide were reported to WHO in 2017, the lowest level since the start of the systematic global data collection 75 years ago (4). However, the incidence is suspected to be under reported due to different elements. The Democratic Republic of Congo (DRC) bears the majority of disease burden (83–84% of the reported cases in 2012, 2015 and 2016 (4). In view of the success in control of the disease, T. b. gambiense was included in the WHO 'roadmap' for elimination and control of neglected tropical diseases. A target date was set for global elimination of HAT as a public health problem (<1 case/10 000 inhabitants in at least 90% of endemic areas) by 2020 with complete interruption of transmission in Africa targeted for 2030 (5).

Bénéfices

Evidence of efficacy is based on data from three (yet to be published) clinical efficacy and safety studies (DNDiFEX004, DNDiFEX005, and DNDiFEX006), using data from 749 patients with HAT (from study sites in DRC and Central African Republic), 619 of which were treated with fexinidazole. FEX006 included 125 paediatric patients aged between 6 and 15 years weighing 20 kg or more. FEX004 compared fexinidazole and NECT in 394 adult patients (aged ≥15 years) with late stage 2 HAT. The success rate was 91.2% for fexinidazole and 97.6% for the NECT combination. The primary objective of the study was met. Fexinidazole was considered an acceptable treatment as the difference in response compared to NECT was <13% in favour of NECT at 18 months after the end of treatment (EOT). In the primary analysis, the difference in success rate between groups remained within the margin of acceptable difference (−6.4%, 97.06% CI −11.2% to −1.6%). However, in the sub-population of patients with cerebrospinal fluid white blood cell count (CSF-WBC) >100 /µL the efficacy was 86.9% in the fexinidazole arm versus 98.7%% in the NECT arm, and therefore the risk of failure was higher in this sub-group with fexinidazole. The follow-up analysis of the success rate at 24 months on the complete population (n=389) yielded similar findings to those with partial data for 24 months at the primary analysis timepoint (n=345) with only two new failures (one in each group). FEX005 was an open-label single-arm cohort study of efficacy and safety of fexinidazole in 230 adult patients with stage 1 or early stage 2 HAT. The success rate with fexinidazole at 12 months after the EOT (98.7%; 95%CI 96.2% to 99.7%), was greater than an unacceptable rate of 80%. No difference was seen in efficacy at 12 months according to the stage of the disease. The success rate at 18 months improved slightly between the initial and follow-up analysis due to the inclusion of the additional 69 patients in the follow-up analysis (all successes): 97.8% (95%CI 95.0 to 99.3) vs 96.9% (95%CI 92.9 to 99.0) in the initial analysis. FEX006 was an open-label single-arm prospective study of efficacy and safety of fexinidazole in 125 children aged ≥6 years and <15 years weighing over 20 kg with any stage HAT. The success rate with fexinidazole at 12 months after the EOT (97.6%; 95%CI 93.1% to 99.5%) was greater than an unacceptable rate of 80% and compatible with a target rate of 92%. The success rate at 18 months improved slightly between the initial and follow-up analysis due to the inclusion of the additional 40 patients in the follow-up analysis (all successes): 98.4% (95%CI 94.3 to 99.8), vs 97.6% (95%CI 91.8% to 99.7%) in the initial 12-month analysis.

Torts

Pooled analyses of data from FEX004, FEX005 and FEX006, revealed findings consistent with observations from the individual study analyses, with regard to the incidence of treatment emergent adverse events (TEAEs), TEAEs that occurred between baseline and end of hospitalization (EOH), TEAEs that occurred after EOH, and TEAEs that were considered by the Investigator as possibly related to treatment. A total of 577 of 619 (93%) patients experienced TEAEs. Overall, 506 of 619 (82%) patients reported a total of 2026 possibly related TEAEs between initiation of treatment and EOT, with most being mild or moderate. In study FEX004 in patients with late stage 2 disease, the overall incidence of TEAEs was comparable between treatment groups (93.6% with fexinidazole vs 92.3% with NECT). The most commonly reported TEAEs across all fexinidazole-treated patients (≥10% of patients) were vomiting (42%), headache (37%), nausea (35%), asthenia (27%), insomnia (23%), tremor (22%), decreased appetite (20%), dizziness (19%), dyspepsia (14%) and feeling hot (10%). Comparing overall TEAEs between fexinidazole and NECT in late stage 2 patients, there were notable differences between treatment groups; these included higher rates in the NECT arm of pyrexia, chills, hyperkalaemia, convulsions and procedural pain; and higher rates in the fexinidazole arm of insomnia, tremor,

headache, asthenia, nausea, dizziness, hypocalcaemia, feeling hot, hypoalbuminaemia, abdominal pain (upper), chest pain and dyspepsia. Vomiting was reported in a similar percentage of patients. All other TEAEs occurred with similar frequency with NECT and fexinidazole in late stage 2 HAT patients, suggesting that the AEs were related to the underlying disease or that both treatments were associated with increased risk of the events to similar extents. With regard to risk of QT prolongation, fexinidazole has been associated with QTcF interval increases and its use is contraindicated in patients at risk of QT prolongation, uncorrected electrolyte abnormalities, symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure or family history of sudden death. Central nervous system/psychiatric events as well as emesis/vomiting were observed with fexinidazole treatment. Asymptomatic reversible neutropenia and elevated liver enzymes that were found at different dose regimens in Chagas disease patients were not reported in HAT patients with the treatment regimen used in the HAT studies.

Rapport coût/efficacité

Drugs for HAT are provided free of charge to the WHO via a public–private partnership between WHO/Sanofi (pentamidine, melarsoprol and eflornithine) and WHO/Bayer AG (suramin, nifurtimox). Under a signed agreement between Sanofi and WHO, drugs are donated to WHO, to be used exclusively for the treatment of HAT. Requests for supplies are made to WHO by governments of disease-endemic countries and organizations working in association with these governments. Stock control and shipment of the drugs are undertaken by Médecins sans Frontières-Logistique according to the agreement. Transport costs to countries are paid by Sanofi through its partnership with WHO. Similar to NECT and other HAT drugs, fexinidazole will be distributed free of charge through the WHO Neglected Tropical Diseases Department to national sleeping sickness control programmes (NSSCPs) and from there to treatment centres. The product will not be available through wide logistics of pharmacies or out of the predefined distribution system. No return on investment is expected. With NECT, indirect costs including transport to hospital, food and hospitalization costs are born by the patients. They should be significantly reduced with fexinidazole when patients are not hospitalized and can be treated close to their home.

Directives de l'OMS

Fexinidazole received a positive opinion by the European Medicines Agency (EMA) under Article 58 on 15 November 2018. It is not yet included in the WHO guidelines or any other national guidelines. However, WHO sleeping sickness treatment guidelines will be under revision in order to consider integration of fexinidazole as part of the therapeutic options to treat gambiense HAT.

Disponibilité

Fexinidazole is a new oral treatment for sleeping sickness disease and is not yet distributed. An application for fexinidazole was submitted to European Medicines Agency (EMA) through Article 58 of Regulation (EC) No 726/2004. Article 58 is a mechanism whereby the EMA may give a scientific opinion, in cooperation with the WHO, for the evaluation of medicinal products intended to prevent or treat diseases of major public interest and exclusively intended for markets outside the European Community. A positive opinion from EMA was given on 15 November 2018 for the following indication: “Fexinidazole Winthrop is indicated for the treatment of both the firststage (haemo-lymphatic) and the 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” However, lower efficacy of fexinidazole as compared to NECT has been seen in a sub-group of patients. Patients with cerebrospinal fluid white blood count (CSF-WBC) >100/µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated. Registrations in DRC and Uganda are also scheduled. Further registrations in other endemic African countries are not planned due to the specific registration regulatory picture for human African trypanosomiasis products and related distribution systems.

Autres considérations

Since 2009, NECT has become the first-line therapy for stage 2 HAT due to T. b. gambiense and has improved the prognosis of treated patients (6), replacing monotherapy with eflornithine. NECT treatment requires a minimum health infrastructure and personnel to administer two slow infusions every day for seven days, on top of an oral treatment every 8 hours for 10 days, requiring systematic hospitalization, as well as being resource consuming for skilled health staff in the environment in which HAT patients live (remote, poor areas with little health infrastructure). NECT is not recommended for early stage disease, instead, patients are treated with pentamidine administered via intramuscular injections. Second line-therapy for stage 2 HAT due to T. b.

gambiense includes melarsoprol, an organoarsenic compound, which is highly toxic and to which resistance has developed (7). Intravenous injections of melarsoprol are painful and can cause phlebitis. The drug has been administered by use of lengthy and complicated dosing schedules, however, an abbreviated 10-day regimen of melarsoprol has been developed. The limitations associated with current HAT therapy include mandatory hospitalization and need for equipment and skilled and trained health staff to administer IV infusions and/or injections. The repeated infusions needed with current HAT therapy are not only painful but increase the risk of infection for the patient. The distribution of treatment to remote health facilities due to heavy components (38 kg per box which includes four treatments comprising drugs, solvents and equipment), is also a costly logistical challenge (8). Fexinidazole is orally administered once daily with food for 10 days. Recommended dosage regimens are according to body weight.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017. (WHO Technical Report Series, No. 1006). Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
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3. Simarro PP, Diarra A, Ruiz Postigo JA, Franco JR, Jannin JG. The human African trypanosomiasis control and surveillance programme of the World Health Organization 2000-2009: the way forward. PLoS Negl Trop Dis. 2011;5(2):e1007.
4. Global Health Observatory data repository - Number of new reported cases (T.b. gambiense) - Data by country [website]. Last updated 20 September 2016. Geneva: World Health Organization; 2016. (http://apps.who.int/gho/data/node.main.A1636, accessed 30 October 2019).
5. Control and surveillance of human African trypanosomiasis: report of a WHO Expert Committee 2013. WHO Technical Report Series, No. 984. Geneva: World Health Organization; 2013.
6. Simarro PP, Franco J, Diarra A, Postigo JA, Jannin J. Update on field use of the available drugs for the chemotherapy of human African trypanosomiasis. Parasitology. 2012;139(7):842–6.
7. Bisser S, N'Siesi FX, Lejon V, Preux PM, Van Nieuwenhove S, Miaka Mia Bilenge C et al. Equivalence trial of melarsoprol and nifurtimox monotherapy and combination therapy for the treatment of second-stage Trypanosoma brucei gambiense sleeping sickness. J Infect Dis. 2007;195(3):322–9.
8. Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Ruiz-Postigo JA, et al. Mapping the capacities of fixed health facilities to cover people at risk of gambiense human African trypanosomiasis. Int J Health Geogr. 2014;13:4.