I.6 Fexinidazole – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Fexinidazole merits inclusion on the WHO Model List of Essential Medicines for the treatment of *Trypanosoma brucei rhodesiense* (r-HAT) due to its high public health relevance and strong benefit-risk profile. r-HAT is a rare but acute and deadly neglected tropical disease affecting vulnerable populations in East and Southern Africa. Fexinidazole offers the first all-oral treatment effective for both stages of r-HAT in adults and children (≥6 years, ≥20 kg), simplifying care delivery in remote settings. Clinical trial data show high cure rates (97–100%) with no deaths attributable to the drug and only mild to moderate adverse events. The medicine is included in the 2024 WHO guidelines, approved by EMA and DRC, and distributed free of charge through a WHO–Sanofi partnership. Its oral administration eliminates the need for toxic injectable drugs like melarsoprol, reduces hospitalization, and expands access to underserved areas. These advantages justify strong support for its inclusion.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) Yes, 7 recommendations and 6 medicines (Eflornithine, Fexinidazole, Melarsoprol, Nifurtimox, Pentamidine, Suramin sodium)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) Yes, adequate evidence exists to support the efficacy and effectiveness of fexinidazole for the treatment of *Trypanosoma brucei rhodesiense* human African trypanosomiasis (r-HAT) in both first-stage and second-stage disease. **Clinical Evidence** The primary evidence stems from the DNDi-FEX-07-HAT study, a Phase II/III, open-label, single-arm clinical trial conducted in Malawi and Uganda. This study enrolled 45 patients, including both adults and children aged ≥6 years and weighing ≥20 kg, with confirmed r-HAT. Of these, 10 patients had first-stage disease, and 35 had second-stage disease . Key findings include: • First-stage r-HAT: All 10 patients achieved treatment success at both the end of hospitalization and at 12-month follow-up, with no	☒ Yes ☐ No ☐ Not applicable

relapses reported.

- Second-stage r-HAT: Out of 35 patients, 34 (97%) achieved treatment success at the end of hospitalization. At 12-month follow-up, the treatment success rate remained high, with only one reported relapse .

These results demonstrate that fexinidazole is highly effective in treating both stages of r-HAT, with sustained efficacy observed over a 12-month period.

Comparative Effectiveness

While the DNDi-FEX-07-HAT study was non-randomized, its outcomes are comparable to historical data from treatments like melarsoprol, which has been associated with higher toxicity and mortality rates. The favorable safety profile and oral administration route of fexinidazole offer significant advantages over existing therapies .

Table 5 - Efficacy outcome at the primary endpoint - Fatality rate at EOH- Study DNDi-FEX-07-HAT

Analysis	Primary endpoint at EOH Study DNDi-FEX-07-HAT
Primary analysis	
EP population, N = 34 n (%) [90% CI][a]	0 (0.0%) [0.00%; 8.43%], p = 0.048788[b]
Sensitivity analysis	
mITT population, N = 35	0 (0.0%) [0.00%; 8.20%], p = 0.04464
TC population, N = 34 n (%) [90% CI][a]	0 (0.0%) [0.00%; 8.43%], p = 0.048788[b,c]
Supplementary analysis	
Total population[d] N = 44 n (%) [90% CI][a]	0 (0.0%) [0.00%; 6.58%], p = 0.020069[b]

Abbreviations: **CI**, confidence interval; **EOH**, end of hospitalization; **EP**, evaluable patient; **mITT**, modified intention-to-treat; **r-HAT**, human African trypanosomiasis due to *T. b. rhodesiense;* **TC**, treatment completers

Source: Study DNDi-FEX-07-HAT Final CSR, Table 17, Table 18 and Table 19

a Clopper-Pearson 90% CI

b Comparison to the pre-specified threshold was done using a one-sided exact test at the 0.05 significance level

c In non evaluable patient (Patient No. 1035 who died during hospitalization) the fatality rate was of 2.86% [90% CI: 0.15% to 12.85%]

d Total population (includes both stage-2 (N= 34) and stage-1 (N = 10) r-HAT patients

Regulatory and Guideline Endorsements

The European Medicines Agency (EMA) adopted a positive opinion on fexinidazole for the treatment of r-HAT in December 2023 .

Subsequently, the World Health Organization (WHO) updated its treatment guidelines in 2024 to recommend fexinidazole as the first-line treatment for r-HAT **The evidence from the DNDi-FEX-07-HAT study, supported by regulatory approvals and guideline updates, confirms the efficacy and effectiveness of fexinidazole for treating both stages of r-HAT. Its oral administration simplifies treatment protocols and enhances accessibility, making it a valuable addition to the therapeutic options for this neglected tropical disease.**	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) Yes, adequate evidence exists to support the safety of fexinidazole for the treatment of *Trypanosoma brucei rhodesiense* human African trypanosomiasis (r-HAT) in both first-stage and second-stage disease. **Clinical Safety Evidence** The primary safety data for fexinidazole in r-HAT patients come from the DNDi-FEX-07-HAT study, a Phase II/III, open-label, single-arm clinical trial conducted in Malawi and Uganda. This study enrolled 45 patients, including both adults and children aged ≥6 years and weighing ≥20 kg, with confirmed r-HAT. Key safety findings include: • Adverse Events (AEs): The majority of AEs were mild to moderate, including gastrointestinal symptoms such as nausea and vomiting, and neurological symptoms like headache. • Serious Adverse Events (SAEs): No SAEs were attributed to fexinidazole. • Mortality: There were no deaths reported during the study period. These findings indicate a favorable safety profile for fexinidazole in the treatment of r-HAT. **Supporting Safety Data from g-HAT Studies** Additional safety data are available from studies on *Trypanosoma brucei gambiense* human African trypanosomiasis (g-HAT), which provide relevant insights due to the similarities in disease pathology and treatment response. (US FDA) • Adult g-HAT Study: In a pivotal multicenter, randomized, non-inferiority trial, fexinidazole demonstrated a safety profile comparable to existing treatments, with most AEs being mild to moderate. • Pediatric g-HAT Study: A multicenter, single-arm, open-label Phase II/III trial involving 125 children aged 6 to 15 years reported that 93% of patients experienced treatment-emergent adverse events, primarily mild or moderate. The most common AEs were vomiting (69%) and headache (33%). No new safety issues were observed beyond those found in adult trials **Regulatory and Guideline Endorsements** The European Medicines Agency (EMA) adopted a positive opinion on fexinidazole for the treatment of r-HAT in December 2023 . Subsequently, the World Health Organization (WHO) updated its treatment guidelines in 2024 to recommend fexinidazole as the first-line	☒ Yes ☐ No ☐ Not applicable

treatment for r-HAT . **The safety profile of fexinidazole is well-established through clinical trials in both r-HAT and g-HAT populations. The evidence indicates that fexinidazole is a safe treatment option for r-HAT, with most adverse events being mild to moderate and no new safety concerns identified. This supports its inclusion in the WHO Model List of Essential Medicines for the treatment of r-HAT.**	

Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?
 	
Yes, fexinidazole has a favourable and meaningful balance of benefits to harms for the treatment of *Trypanosoma brucei rhodesiense* (r-HAT) in both the first and second stages of disease, particularly in adults and children ≥6 years old and ≥20 kg in weight.
 	
Benefits
• Efficacy: In the DNDi-FEX-07-HAT trial (N=45), fexinidazole demonstrated:
  ○ 0% mortality at end of hospitalization (primary endpoint in stage-2 r-HAT)
  ○ 97% cure rate at 12 months in stage-2 patients
  ○ 100% cure rate in stage-1 patients
  ○ All relapses were rare and manageable with rescue therapy (e.g., melarsoprol)
• Ease of administration:
  ○ First oral treatment for r-HAT, reducing the need for hospitalization, intravenous access, and complex logistics
  ○ Enables community-level treatment, especially beneficial in low-resource settings
• Improves adherence and access: Simple 10-day oral regimen, supervised or home-based with trained personnel
 	
Harms
• Mild to moderate adverse events: Mostly gastrointestinal (vomiting, gastritis) and minor ECG changes (U-wave abnormalities, QT prolongation <500 ms)
• No deaths or serious adverse events attributed to fexinidazole
• No neuropsychiatric or long-term safety concerns emerged in r-HAT patients
 	
Supporting Endorsements
• WHO 2024 treatment guidelines recommend fexinidazole as first-line for r-HAT in eligible populations
• EMA approval for the rhodesiense indication granted in 2023
• Support from DNDi and WHO NTD Department, with pharmacovigilance plans in place
 	
The favorable safety profile, high efficacy, and operational advantages of fexinidazole—particularly its oral formulation and effectiveness in both stages of r-HAT—strongly support its positive benefit-risk balance. Given the severe harms and logistical challenges of current alternatives (e.g., melarsoprol's encephalopathy risk), fexinidazole represents a significant therapeutic advance for a neglected population.
	☒ Yes ☐ No ☐ Not applicable

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable

Yes, there are specific requirements for the safe, effective, and appropriate use of fexinidazole in the treatment of *Trypanosoma brucei rhodesiense* human African trypanosomiasis (r-HAT). These include diagnostic, treatment supervision, and patient monitoring protocols, as detailed below:

1. Diagnostic Requirements

- Microscopic confirmation of trypanosomes in blood or cerebrospinal fluid (CSF) is required for diagnosis of r-HAT, as no rapid diagnostic or serological tests currently exist for this form.
- CSF examination (lumbar puncture) is not required to start fexinidazole in eligible patients (≥6 years, ≥20 kg), but:
    - It is required for patients under 6 years old, <20 kg, or with contraindications to fexinidazole, to guide therapy selection (e.g., suramin vs. melarsoprol).

2. Treatment Administration Requirements

- Daily administration with food is essential to ensure optimal drug absorption.
- Trained health staff must:
    - Verify that the patient is in a fed state.
    - Directly observe drug intake (whether in facility or at home, under supervision).
- For certain patients (e.g., psychiatric history, children <35 kg), inpatient administration is advised to reduce risk of poor adherence or complications.

3. Monitoring and Follow-up

- Patients should be monitored closely during the 10-day treatment, especially for:
    - Vomiting shortly after dosing (risk of reduced efficacy)
    - ECG abnormalities (QT prolongation, U-wave changes)
- Follow-up at 12 months post-treatment is recommended to detect possible relapses.
    - Patients must be informed about signs of relapse and instructed to report symptoms such as fever, fatigue, or neurological issues.

4. Health Provider Training

• Providers must be trained in:
  ○ Diagnosis of HAT, including use of microscopy and CSF analysis
  ○ Management of side effects (e.g., gastrointestinal reactions, ECG interpretation)
  ○ Counseling patients and families on adherence, nutrition during treatment, and signs of relapse
 	
Safe and effective use of fexinidazole requires a minimum health system infrastructure with diagnostic microscopy, supervised oral treatment, provider training, and structured patient follow-up. These are feasible in many endemic areas and represent a major simplification compared to the invasive and toxic alternatives like melarsoprol.	

Are there any issues regarding price, cost-effectiveness and budget implications in different settings?
 	
No, there are no major issues regarding price, cost-effectiveness, or budget implications associated with fexinidazole for the treatment of *Trypanosoma brucei rhodesiense* (r-HAT), due to its inclusion in a donation-based access model and its operational advantages over existing therapies.
 	
1. Cost and Access
• Fexinidazole is provided free of charge through a long-standing public–private partnership between Sanofi and WHO.
• Sanofi donates fexinidazole to WHO, and the drugs are distributed:
  ○ Exclusively to National Sleeping Sickness Control Programs (NSSCPs)
  ○ Through Médecins Sans Frontières-Logistique, with shipping costs covered by Sanofi
• This zero-cost drug model significantly reduces direct treatment costs for governments and implementing partners.
 	
2. Cost-Effectiveness
• Fexinidazole replaces intravenous treatments (suramin and melarsoprol), which:
  ○ Require prolonged hospitalization (up to a month for melarsoprol)
  ○ Involve higher costs for equipment, supplies, and staff
  ○ Are associated with severe adverse events requiring intensive care
• Fexinidazole is oral, short-course (10 days), and outpatient-friendly, leading to:
  ○ Reduced inpatient burden and logistics
  ○ Lower overall health system costs
  ○ Improved reach to rural and hard-to-reach populations
 	
3. Implications in Different Settings
• Low-income and remote settings benefit disproportionately from fexinidazole:
	☐ Yes ☒ No ☐ Not applicable

○ Less reliance on tertiary hospitals ○ Easier integration into primary care ○ Minimization of patient and caregiver travel and accommodation costs • No return on investment is expected from the donor or manufacturer, and there are no plans to commercialize the product through regular pharmacies, maintaining its public health mission. Fexinidazole has clear cost-effectiveness advantages over current standard treatments and imposes no direct budgetary burden on endemic countries due to its donation-based distribution model. This makes it a highly suitable and sustainable option for widespread use in the management of r-HAT.	
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) **Yes,** fexinidazole is available and accessible across countries **where *Trypanosoma brucei rhodesiense* (r-HAT) is endemic, thanks to a dedicated global access mechanism coordinated by WHO and its partners.** **1. Availability and Distribution Model** Fexinidazole is not commercially distributed **through pharmacies or standard procurement systems.** **It is provided** free of charge **via a** WHO–Sanofi donation program **under a public–private partnership established in 2001 and renewed every 5 years.** **Distribution is handled by** Médecins Sans Frontières (MSF)–Logistique **under WHO's coordination.** **How it works:** **Endemic countries submit** requests to WHO's NTD department**.** **WHO coordinates delivery to** National Sleeping Sickness Control Programs (NSSCPs)**.** **Drugs are then shipped directly to** designated treatment centers**.** **This mechanism ensures** secure and equitable access **while bypassing traditional commercial supply chains.** **2. Registration and Regulatory Approval** • Fexinidazole is approved by at least one Stringent Regulatory Authority (SRA) – the European Medicines Agency (EMA) under Article 58. • It is also registered in the Democratic Republic of Congo (DRC), Uganda, and the USA. • For other countries, importation is authorized via WHO letters of interest and inclusion in national treatment policies, rather than through national registration processes. **3. No Known Shortages** • There have been no reported shortages of fexinidazole for HAT since its introduction. • A controlled distribution system and WHO stockpile management reduce the risk of stock-outs.	☒ Yes ☐ No ☐ Not applicable

4. Generics and Biosimilars • There are no generic or biosimilar versions of fexinidazole currently available. • All production and supply are managed by Sanofi, which holds the rights and coordinates with WHO for non-profit distribution. Fexinidazole is **readily accessible across endemic countries** through a **dedicated WHO access program**. Its **non-commercial, donation-based model** ensures free and consistent supply without reliance on national regulatory bottlenecks or market forces. This makes it **highly accessible despite its niche use** for a neglected tropical disease.	
Does the medicine have wide regulatory approval? **Fexinidazole does not yet have wide regulatory approval,** but it holds approvals in key jurisdictions that enable its distribution and use across endemic countries through WHO-coordinated mechanisms. **Approved by a Stringent Regulatory Authority (SRA)** • European Medicines Agency (EMA): Fexinidazole received a positive opinion under Article 58 (now EU Regulation 2019/6 Article 110), which allows the EMA to provide scientific opinions for medicines intended exclusively for markets outside the EU. o First approved in 2018 for *T.b. gambiense* HAT o Extended in December 2023 to include *T.b. rhodesiense* (r-HAT) **National Regulatory Approvals** • Democratic Republic of Congo (DRC): Approved for both *gambiense* and *rhodesiense* HAT. First in 2018 for *g-HAT*; extended in May 2024 for *r-HAT*. • Uganda: Submitted in May 2024; pending or under review at the time of application submission. • United States (US): Approved under a special use provision, not for commercial distribution, but recognized for emergency or traveler cases. **Not Registered in All Endemic Countries** • Many endemic countries do not require local registration for fexinidazole due to: o Its approval by an SRA o Its distribution exclusively through WHO's donation-based program o Use governed by national HAT control programs and inclusion in national treatment guidelines following WHO endorsement **Access Mechanism Bypasses Regulatory Delays** • Instead of requiring full registration in each country, fexinidazole is imported based on:	☐ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable

○ Inclusion in national policy ○ Letter of interest from health authorities to WHO While fexinidazole does not have wide registration in national regulatory agencies, it has sufficient regulatory endorsement (EMA, DRC, USA) and WHO guideline support to facilitate global access via non-commercial, centrally managed channels. This model is effective for neglected diseases where market incentives are low but public health need is high.	