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ADISINSIGHT REPORT

Fexinidazole: First Global Approval

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Abstract
Fexinidazole Winthrop (hereafter referred to as fexinidazole) is a DNA synthesis inhibitor developed by the Drugs for Neglected Diseases initiative (DNDi), in collaboration with Sanofi, for the oral treatment of human African trypanosomiasis (HAT) [commonly known as 'sleeping sickness'] and Chagas' disease. The drug is a 5-nitroimidazole derivative first discovered by Hoechst AG (now part of Sanofi) and was identified by the DNDi in 2005 as having activity against *Trypanosoma brucei gambiense* and *T. b. rhodesiense*. Under Article 58 of Regulation (EC) no. 726/2004 (a regulatory mechanism for reviewing new medicines destined for use outside of the EU), fexinidazole has been granted a positive opinion by the EMA for the treatment of both the first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of HAT due to *T. b. gambiense* (g-HAT) in adults and children aged ≥ 6 years and weighing ≥ 20 kg. This approval will facilitate and support marketing authorization application in endemic countries in 2019; following registration, fexinidazole will be distributed via the WHO to endemic countries for g-HAT. Phase 3 evaluation of fexinidazole for g-HAT is ongoing in the Democratic Republic of the Congo and Guinea and the drug is also in development for Chagas' disease, with a study currently ongoing in Spain. Clinical development for visceral leishmaniasis is discontinued. This article summarizes the milestones in the development of fexinidazole leading to this first approval for g-HAT.

1 Introduction

Diseases caused by kinetoplastid parasites are a chronic challenge for many developing countries [1]. These diseases include trypanosomiasis, referred to as human African trypanosomiasis (HAT) [or 'sleeping sickness'] in Africa and Chagas' disease in Latin America, and leishmaniasis. Parasites of the genus *Trypanosoma* are the etiological agents of trypanosomiasis. *Trypanosoma brucei gambiense* is responsible for most cases of HAT (referred to hereafter as g-HAT) and *T. b. rhodesiense* for the more virulent HAT cases; both forms have two stages, with the first being a haemo-lymphatic phase in which parasites invade the blood and lymphatic system, and the second being a meningo-encephalitic phase in which parasites penetrate the blood–brain-barrier and eventually cause death if not treated [1]. By contrast, the causative agent of Chagas' disease is *Trypanosoma cruzi* and various species of *Leishmania* are responsible for causing leishmaniasis (of which there are visceral, cutaneous and mucosal forms) [1].

As these kinetoplastid diseases have historically attracted little pharmaceutical industry interest, the available treatment options are few and limited by factors such as variable/unsatisfactory efficacy, parenteral administration, toxicity and/or long administration duration [1, 2]. Although the combination regimen of nifurtimox plus eflornithine (NECT) was a therapeutic improvement for g-HAT (e.g. relative to the long, complex intravenous infusion protocol of eflornithine and the toxicity of melarsoprol) [1], it requires patients to have a lumbar puncture to determine the HAT stage (as its use is limited to stage 2) and is administered via several intravenous infusions [3]. However, increased funding/interest in recent years has resulted in application of modern drug development strategies in this therapeutic area and a number of new potential therapies [1].

Fexinidazole Winthrop (hereafter referred to as fexinidazole) is a 5-nitroimidazole derivative DNA synthesis inhibitor developed by the Drugs for Neglected Diseases initiative (DNDi), in collaboration with Sanofi, for the oral

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through preclinical and clinical studies to market launch and beyond.

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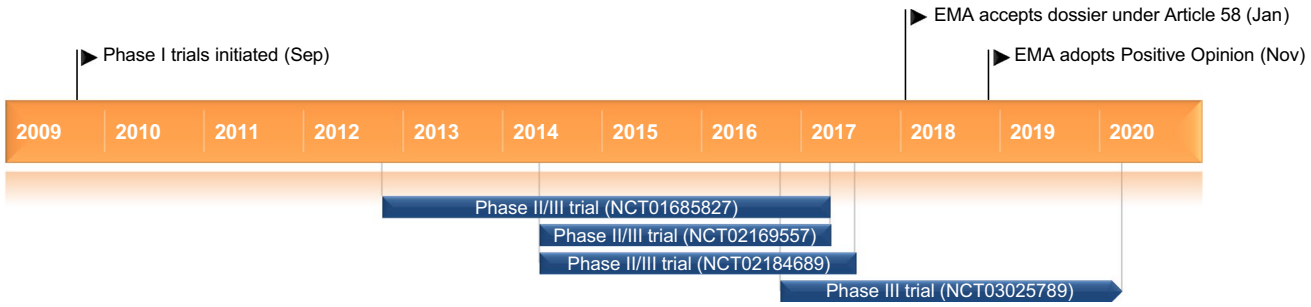


Key milestones in the development of fexinidazole, focussing on its use in human African trypanosomiasis caused by *Trypanosoma brucei gambiense*. *EMA* European Medicines Agency

treatment of HAT [4]. In November 2018, the EMA (under Article 58, which allows the EMA to give scientific opinion, in collaboration with the WHO and relevant non-EU authorities, on medicines intended for markets outside the EU [5]) adopted a positive opinion of fexinidazole for the treatment of both first- and second-stage g-HAT in adults and children aged ≥ 6 years and weighing ≥ 20 kg [6]. This approval will facilitate and support marketing authorization application in endemic countries in 2019 [7]. Fexinidazole is the first all-oral treatment for g-HAT and is appropriate for both the first and second stage of the disease, thus likely reducing the need for patient hospitalization and lumbar punctures. Phase 3 evaluation of fexinidazole for g-HAT is ongoing in the Democratic Republic of the Congo and Guinea, and the drug is also in development for Chagas' disease, with a study currently ongoing in Spain. Clinical development for visceral leishmaniasis has been discontinued due to lack of efficacy [8].

1.1 Company Agreements

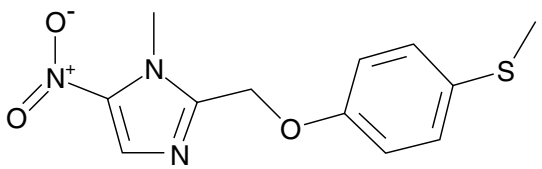
DNDi's fexinidazole program is supported by grants from a number of government and public financial institutions and private foundations, including UK aid, Swiss Development Cooperation, Médecins Sans Frontières, the Bill and Melinda Gates Foundation, French Development Agency, German Federal ministry of Education and Research through KfW Development Bank, Dutch Ministry of Foreign Affairs, the Republic and Canton of Geneva, Stavros Niarchos Foundation, Brian Mercer Charitable Trust, the UBS Optimus Foundation, French Ministry of European and Foreign Affairs, German Corporation for International Cooperation on behalf of the German Government, Spanish Agency for International Development Cooperation and Norwegian Agency for Development Cooperation [4, 9].

In 2009, the DNDi entered into an agreement with Sanofi to develop fexinidazole, with the DNDi being responsible for its preclinical, clinical and pharmaceutical development and Sanofi being in charge of its industrial development, registration and manufacture [3]. Fexinidazole, like other anti-HAT medicines, will be donated by Sanofi to the WHO for free distribution to disease endemic countries [10].

2 Scientific Summary

2.1 Pharmacodynamics

Fexinidazole creates reactive amine species which are indirectly toxic and mutagenic to trypanosomes [6]. Fexinidazole was active against *T. b. gambiense* and various other *T. b.* subspecies (including *T. b. rhodesiense* and *T. b. brucei*) in vitro, with its sulfoxide (M1) and sulfone (M2) metabolites demonstrating broadly similar trypanocidal activity [11, 12]. Fexinidazole demonstrated curative capacity in murine models of these trypanosomal infections, including acute infections with *T. b. gambiense* [11] or *T. b. rhodesiense* [11, 12] and chronic infections with *T. b. brucei* [11–13], the latter of which is a model for stage 2 HAT. Fexinidazole was likewise active in mouse models of Chagas' disease caused by various strains of *T. cruzi* (susceptible, resistant or partially resistant to the current standard treatment benznidazole) [14], with the drug appearing to have greater



Chemical structure of fexinidazole

benefit against chronic than acute *T. cruzi* infection in a similar in vivo mouse model [15]. In terms of other parasites, fexinidazole was active against *Leishmania donovani* in a mouse model of visceral leishmaniasis [16], displayed in vitro activity against *Trypanosoma lewisi* (comparable

Features and properties of fexinidazole	
Alternative names	Fexinidazole Winthrop; HOE-239
Class	Antiparasitics; nitroimidazoles
Mechanism of action	DNA synthesis inhibitor
Route of administration	Oral
Pharmacodynamics	Active against *Trypanosoma brucei* subspecies (including *T. b. gambiense, T. b. rhodesiense* and *T. b. brucei*) in vitro and demonstrates curative capacity in murine models of these trypanosomal infections
	Active in mouse models of Chagas' disease and visceral leishmaniasis and against *T. lewisi* infection in immunocompromised rats
Pharmacokinetics	Quickly absorbed and metabolized to two active metabolites; all three molecules cross the blood : brain barrier
Most frequent adverse events	Headache, vomiting, insomnia, nausea, asthenia, tremor and decreased appetite
Chemical name	1-Methyl-2-((4-(methylthio)phenoxy)methyl)-5-nitro-1H-imidazole

to its activity against *T. b. gambiese*) [17] and was active against *T. lewisi* infection in immunocompromised rats [17].

There does not appear to be any cross-reactivity between fexinidazole and its sulfoxide and sulfone metabolites, or between these molecules and other trypanosomal drugs used in humans, such as eflornithine, pentamidine or melarsoprol, in terms of in vitro trypanosomal activity [12]. Of note, fexinidazole potentiated the benefit of melarsoprol in some instances when gel preparations of the drugs were used in combination in a mouse model of chronic trypanosome infection [18]. Fexinidazole is mutagenic to bacteria when assessed by the Ames test, but does not display mammalian mutagenic potential in in vitro, in vivo or ex vivo assays [11, 19]. Unlike other drugs available for HAT, fexinidazole displays little if any non-specific cytotoxicity [11].

2.2 Pharmacokinetics

Several studies (including three first-in-human studies) have assessed the pharmacokinetics of fexinidazole (as tablets or suspension) in healthy male subjects of sub-Saharan origin [20]. Limited pharmacokinetic data are available for fexinidazole in adults with stage 2 g-HAT in a phase 2/3 trial conducted in sub-Saharan countries (NCT01685827) [21].

After a single oral dose of fexinidazole (100–3600 mg, as tablets or suspension) in healthy subjects, fexinidazole was quickly absorbed, with maximum plasma concentrations (C_{max}) of the drug and its sulfoxide metabolite being reached within a median of 2–6 h; the major sulfone metabolite took longer to reach C_{max} (median 14–24 h post-dose) [20]. The absorption kinetics of fexinidazole in a multiple-dose study (in which the drug was administered as tablets for 14 days at doses of 1200–3600 mg in fasted healthy subjects) were generally consistent with these findings. Absorption of fexinidazole and its metabolites was less than dose-proportional in these trials [20].

Administration of fexinidazole tablets with food (regardless of type) increased exposure to the drug ≈ 3- to 5-fold relative to fasted administration in single-dose studies, with proportional increases in the sulfoxide and sulfone metabolites also evident [20].

According to a subsequent healthy subject study designed to determine the most appropriate fexinidazole dosing schedule, administration of fexinidazole tablets with food, at a dose of 1800 mg for 4 days followed by 1200 mg for 6 days, could provide sulfone plasma concentrations ≥ 10,000 ng/mL for ≥ 6 days (day 4–10) in most patients; such plasma concentrations of sulfone were associated with cure in the *T. b. brucei* murine model of chronic infection [20]. Fexinidazole and its sulfoxide metabolite reached C_{max} a median 4 h after fexinidazole administration, regardless of the day of dosing assessed (i.e. day 1, 4, 7 or 10), whereas the sulfone metabolite reached C_{max} a median 23 h after the initial dose and 3–6 h after administration of the drug on days 4, 7 and 10 [20]. Achievement of target exposure was confirmed with this fexinidazole regimen in a phase 2/3 trial in adults with g-HAT [21].

Blood–brain-barrier penetration is a necessary property for a drug intended to treat stage 2 HAT. Fexinidazole and/or its sulfoxide and sulfone metabolites were present in the brains of rodents after oral dosing [11, 13], with the brain : plasma concentration ratios for the respective molecules being 1.8, 0.18 and 0.13 in infected animals [13]. Multiple CYP isoenzymes appear to be involved in metabolizing fexinidazole (including CYP1A2, CYP2B6, CYP2C19, CYP3A4, CYP3A5 and, to a lesser degree, CYP2D6), making it unlikely that its pharmacokinetics will be impacted significantly by other drugs [11]. Nitroreductase was also shown to be involved in activating fexinidazole and its sulfoxide metabolite in *L. donovani* amastigotes [16].

After single-dose oral administration in healthy subjects, fexinidazole was eliminated almost entirely via non-renal routes, with only 0.8–3.2% of a dose being excreted in the urine over 168 h post-dose; elimination of the drug and its metabolites via the urine was also negligible after multiple doses [20]. Plasma concentrations of fexinidazole declined

Key clinical trials of fexinidazole (Drugs for Neglected Diseases initiative)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Fexinidazole	g-HAT (any stage) in patients aged ≥ 6 years	3	Recruiting	DRC; Guinea	NCT03025789
Fexinidazole	g-HAT (stage 1 or early stage 2) in patients aged ≥ 15 years	2/3	Completed	DRC	NCT02169557
Fexinidazole	g-HAT (any stage) in patients aged 6–14 years	2/3	Completed	DRC	NCT02184689
Fexinidazole vs. NECT	g-HAT (stage 2) in patients aged ≥ 15 years	2/3	Completed	DRC; Congo; Central African Republic	NCT01685827
Fexinidazole vs. placebo	Chronic Chagas' disease in adults	2	Recruiting	Spain	NCT03587766
Fexinidazole vs. placebo	Chronic Chagas' disease in adults	2	Terminated	Bolivia	NCT02498782
Fexinidazole	Visceral leishmaniasis in patients aged 15–60 years	2	Terminated	Sudan	NCT01980199

DRC Democratic Republic of the Congo, *g-HAT* Human African trypanosomiasis caused by *Trypanosoma brucei gambiense*, *NECT* nifurtimox–eflornithine combination therapy

in a multiphasic fashion after single-dose administration; the mean terminal elimination half-life was 9–15 h for fexinidazole, 8–15 h for the sulfoxide metabolite and 18–25 h for the sulfone metabolite [20].

2.3 Therapeutic Trials

Oral fexinidazole was an effective alternative to NECT for the treatment of stage 2 g-HAT in patients aged ≥ 15 years in a pivotal phase 2/3 trial (NCT01685827) [21]. The rate of treatment success 18 months after the end of therapy in the modified intent-to-treat (ITT) population was 91.2% with fexinidazole ($n = 262$) and 97.6% with NECT ($n = 127$), with the between-group difference for this primary endpoint (− 6.4%; 97.06% CI − 11.2 to − 1.6; $p = 0.0029$) being within the margin of acceptable difference of − 13%. Sensitivity analyses in the ITT ($n = 394$) and per-protocol ($n = 388$) populations were consistent with this primary efficacy analysis, as was the failure-free rate at 18 months in the modified ITT (93% with fexinidazole vs. 98% with NECT; based on Kaplan–Meier assessment of time to proven and definitive failure). Treatment failure occurred in 23 fexinidazole recipients [due to disease relapse ($n = 15$), death ($n = 6$), withdrawing consent ($n = 1$), being lost to follow-up or having no lumbar puncture at 18 and 24 months ($n = 1$)] and 3 NECT recipients [due to death ($n = 2$) or having no lumbar puncture at 18 and 24 months ($n = 1$)], most commonly within the first 12 months of completing treatment. This randomized, open-label, noninferiority trial enrolled patients with detectable parasites in at least one bodily fluid (i.e. lymph node fluid or blood) and trypanosomes or > 20 white blood cells/μL in their cerebrospinal fluid. Fexinidazole was administered at a once-daily dosage of 1800 mg on days 1–4 and 1200 mg on days 5–10; the NECT regimen comprised thrice-daily oral nifurtimox (15 mg/kg per day) on days 1–10 and twice-daily intravenous eflornithine (400 mg/kg per day, via 2 h infusion) on days 1–7. Treatment success was defined as being alive, having no evidence of trypanosomes in any body fluids, no requirement for rescue medication, and ≤ 20 white blood cells/μl of cerebrospinal fluid [21].

Two additional phase 2/3 trials support these findings, with 98.7% of patients aged ≥ 15 years with stage 1 or early-stage 2 g-HAT ($n = 230$) [NCT02169557] and 97.6% of children aged 6–14 years with g-HAT of any stage ($n = 125$) [NCT02184689] having treatment success 12 months after completing fexinidazole treatment [3].

2.4 Adverse Events

Oral fexinidazole had an acceptable tolerability profile when used to treat stage 2 g-HAT in patients aged ≥ 15 years in the pivotal phase 2/3 trial (NCT01685827) [21]. Adverse events considered related to treatment were experienced by a large proportion of fexinidazole and NECT recipients (81 vs. 79%), with those that occurred most frequently generally being mild or moderate and more common with fexinidazole than with NECT, with the exception of vomiting (no further details reported). The most common (incidence > 20%) treatment-emergent adverse events (TEAEs) were headache (35% of patients), vomiting (28%), insomnia (28%), nausea (26%), asthenia (23%), tremor (22%) and decreased appetite (21%) with fexinidazole and vomiting (29%) and headache (24%) with NECT. Several of the TEAEs most common with fexinidazole occurred with an incidence significantly ($p < 0.05$) greater than with NECT, including headache (35 vs. 24%), insomnia (28 vs. 12%), asthenia (23 vs. 14%) and tremor (22 vs. 11%). There were also significant ($p < 0.05$) differences between the treatment groups in the incidence of some less common TEAEs, with the difference favouring fexinidazole for some (including convulsion, hyperkalaemia, pyrexia, chills and investigations; 2–10 vs. 8–19% of NECT recipients) and favouring NECT for others (upper abdominal pain, abdominal distension, hypocalaemia, hypoalbuminaemia,

feeling hot, chest pain, anxiety and hypertension; 0–5 vs. 3–14% of fexinidazole recipients) [21].

Only four serious AEs were considered to be possibly related to treatment in this trial; these occurred in three fexinidazole recipients and included two cases of personality change, one case of acute psychosis and one of hyponatraemia [21]. Few fexinidazole or NECT recipients died (3 vs. 2%), with none of the deaths considered treatment related. Fexinidazole was associated with an increase in Fridericia-corrected QT (QTcF) interval of 15–20 min and an increase in heart rate of ≈ 8 beats/min; the QTcF interval was 450–500 ms in 7% of patients treated with fexinidazole versus none of those treated with NECT [21].

Additional phase 2/3 studies in patients aged ≥ 15 years with stage 1 or early-stage 2 g-HAT (NCT02169557) or children aged 6–14 years with g-HAT of any stage (NCT02184689) found no new safety signals with fexinidazole [3].

2.5 Ongoing Clinical Trials

A phase 3 trial evaluating fexinidazole in patients aged ≥ 6 years with g-HAT of any stage treated either as inpatients or outpatients and including pregnant or lactating patients (NCT03025789) was initiated in November 2016 and is estimated to enroll 174 participants and be completed in March 2020. A phase 2 trial assessing fexinidazole in adults with chronic Chagas' disease (NCT03587766) is also underway (initiated November 2017; estimated completion December 2019). An open-label noncomparative clinical study to assess fexinidazole in patients with stage 2 HAT due to *T. b. rhodesiense* [22] is planned to start in Uganda and Malawi in 2019.

3 Current Status

Fexinidazole received a positive opinion from the EMA (under Article 58) on 15 November 2018 for the treatment of first-stage and second-stage g-HAT in adults and children aged ≥ 6 years and weighing ≥ 20 kg, supporting the ongoing registration process in endemic countries and then the distribution by the WHO.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the author on the basis of scientific completeness and accuracy. Emma Deeks is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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