

Case study: Sanofi/DNDi

Sanofi/DNDi use PharmaPendium's Drug-Drug Interaction Risk Calculator (DDIRC) in successful EMA and FDA submissions



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First all-oral treatment for sleeping sickness

Fexinidazole treats Stage 1 and Stage 2 sleeping sickness caused by *Trypanosoma brucei gambiense*.

- For adults and children above the age of six and over 20 kg
- Developed by Sanofi in partnership with the Drugs for Neglected Diseases initiative (DNDi)



Key insights

- A complex metabolism pathway made it challenging to set up a dynamic approach (PBPK model).
- DDIRC identified potential drug interactions simultaneously, saving time and resources.
- DDIRC predictions supported the drug interactions sections of the labelling (SmPC and US PI).



What is PharmaPendium?

PharmaPendium is the most comprehensive database of regulatory-grade data with robust analytics and modeling tools.

- Extracted, searchable data from FDA, EMA, FDA Advisory Committee, FAERS
- A mechanistic static DDI risk calculator (DDIRC)

Challenge

Finding the data to support regulatory submissions is difficult. When researchers manually find, review and interpret data, they can miss critical information.

To support its regulatory submissions for the new drug fexinidazole, Sanofi/DNDi needed to assess the risk of drug-drug interactions on potential co-medications.

Solution

Sanofi/DNDi used PharmaPendium's DDIRC to predict drug-drug interactions. The results of in vivo simulations were used to characterize the risk of in vivo interaction of fexinidazole with co-medications in the drug interaction and PK sections of its labelling. Sanofi/DNDi included these predictions in the dossier submitted to the agencies.

Result

Fexinidazole has been authorized by:

- Food and Drug Administration (FDA)
- Committee for Medicinal Products for Human Use of the European Medicinal Agency
- Democratic Republic of Congo and in Uganda

In their words

On the following pages, read in Sanofi/DNDi's own words how PharmaPendium and its built-in DDIRC supported EMA and FDA authorization of fexinidazole.

Sanofi/DNDi – In their words

DDIRC a model-informed approach to support EMA and FDA submission of fexinidazole (Sanofi/DNDi)

About Fexinidazole

Fexinidazole is the first all-oral treatment for both stages of the *Trypanosoma brucei gambiense* form of sleeping sickness or Human African trypanosomiasis (HAT) in patients 6 years of age and older and weighing at least 20 kg.

Fexinidazole was developed as part of an innovative partnership between the non-profit research and development organization Drugs for Neglected Diseases initiative (DNDi), which conducted the pivotal clinical trials for this treatment, in partnership with the National Sleeping Sickness Programs of the Democratic Republic of Congo (DRC) and Central African Republic (CAR), and Sanofi.

Fexinidazole has been granted a positive opinion by the Committee for Medicinal Products for Human Use of the European Medicinal Agency in accordance with Article 58 of Regulation. Fexinidazole was granted marketing authorization in the Democratic Republic of Congo and in Uganda. Fexinidazole has been authorized by the Food and Drug Administration (FDA).

How DDIRC predictions supported EMA and FDA submissions?

DDIRC was part of the strategy used to assess the risk of in vivo interaction of fexinidazole on other drugs that can be co-prescribed, in addition to an in vivo drug interaction study. The in vivo predictions made with DDIRC were included in the dossier submitted to the Agencies and further discussed with the Agencies based on Questions and Answers. The evaluation of those simulations by the Agencies are included in their evaluation report of fexinidazole dossier: European Public Assessment Report¹ or FDA CDER multidiscipline review². The results of the in vivo simulations were also used to characterize the risk of in vivo interaction of fexinidazole on other drugs in the drug Interaction and PK sections of the labelling of fexinidazole (European Summary Product Characteristics or US Product Information), when this risk was not assessed based on clinical drug interaction data.

More Details

In vitro experimental data

Fexinidazole and one of its active abundant metabolite (M1) have, based on in vitro experiments performed by Sanofi, the potential to competitively inhibit multiple CYP enzymes including CYP3A4, CYP1A2, CYP2C19, and CYP2B6. The in vitro CYP induction study showed that fexinidazole and its metabolite M1 have no significant potential to induce CYP1A2 and CYP3A while a potential for CYP2B6 was observed.

The other abundant and active metabolite M2 did neither inhibit nor induce any CYPs tested.

DDI predictions performed using DDIRC

The potential for in vivo inhibition was estimated using the simple static equations from the FDA guidance on drug interaction³. A risk of in vivo interaction of fexinidazole on other drugs mainly metabolized by CYP1A2, CYP2C19, CYP2D6 and CYP3A4 was predicted by CYP inhibition at the hepatic level as well as at the intestinal level for drugs highly metabolized by CYP3A4 and having significant intestinal 1st pass.

To mitigate those findings, the Drug Drug Interaction Risk Calculator allowing the prediction of in vivo interaction using mechanistic static models was used. The predictions were performed including both fexinidazole and M1 as competitive inhibitor, since the software allows to handle at the same time the in vitro parameters of a parent drug and of its metabolite.

In vitro inhibition and induction experimental results were used to populate DDIRC and predict AUC ratio for more than 300 marketed drugs based on their fraction metabolized values (fm) for CYP3A4, CYP1A2, CYP2C19, CYP2D6 and/or CYP2B6.

DDIRC predictions on the inhibition of CYP1A2 and CYP2C19 by fexinidazole were compared to the results of a clinical drug interaction study performed with caffeine and omeprazole, respectively, and available at that time. The agreement between predicted and observed data validated the approach and gave confidence in the predictions for CYP2D6 and CYP3A4.

DDI predictions submitted to regulatory agencies

The DDI predictions performed with DDIRC were included in the dossier and submitted to EMA and FDA and were used for the drug interaction sections of the labelling. FDA requested some clarifications on the model used and some parameters. As part of the answers, calculation details and DDIRC Support manual were provided to FDA. At the end, predictions of interactions were accepted and used in the labelling of fexinidazole.

The in vitro and vivo drug interaction data and the DDIRC predictions were used to support the drug interactions sections and PK sections of the SmPC and US PI. See below those sections for the US PI⁴.

Why a static mechanistic approach was able to support DDIs labelling?

Because fexinidazole has a complex metabolism pathway involving multiple CYP enzymes and affects also some major CYP enzymes, it was scientifically challenging and resource/time consuming to set up a dynamic approach (PBPK model). The sponsor decided to use a mechanistic static approach that can easily handle multiple CYP enzymes (metabolism and inhibition). Using a minimal qualification with an in vivo interaction study that gave power to the prediction, DDIRC helped to identify potential interactions drugs simultaneously and allowed to refine the drug interaction profile of fexinidazole saving considerable time and resources.

While a PB/PK model requires clinical DDI validation to be approved by regulatory agencies this is not the case for the static approach used in DDIRC as the model is already validated by regulatory agencies (FDA, EMA, and PMDA) within their DDI guidances.

7.2 Pharmacokinetics Drug Interactions

Table 3: Effect of Fexinidazole on other Drugs

Drugs Metabolized by Cytochrome P450 (CYP) 3A4	
<i>Examples (not fully inclusive):</i>	Lovastatin, simvastatin, nisoldipine, saquinavir, midazolam
<i>Clinical Impact</i>	Increased risk for adverse reactions associated with increased concentrations of the drug due to inhibition of CYP3A4 by fexinidazole [see <i>Clinical Pharmacology</i> (12.3)].
<i>Prevention or Management</i>	Avoid concomitant use with Fexinidazole Tablets.
Drugs Metabolized by CYP1A2 or CYP2C19	
<i>Examples (not fully inclusive):</i>	CYP1A2: duloxetine, tacrine, tizanidine, theophylline CYP2C19: lansoprazole, mephenytoin, diazepam
<i>Clinical Impact</i>	Increased risk for adverse reactions associated with increased concentrations of the drug due to inhibition of either CYP1A2 or CYP2C19 by fexinidazole [see <i>Clinical Pharmacology</i> (12.3)].
<i>Prevention or Management</i>	Monitor for adverse reactions associated with these drugs when used concomitantly with Fexinidazole Tablets.
Drugs Metabolized by CYP2B6	
<i>Examples (not fully inclusive):</i>	Bupropion, efavirenz
<i>Clinical Impact</i>	Increased risk for the lack of efficacy associated with decreased plasma concentrations of the drug due to induction of CYP2B6 by fexinidazole [see <i>Clinical Pharmacology</i> (12.3)].
<i>Prevention or Management</i>	Avoid concomitant use with Fexinidazole Tablets. If coadministration cannot be avoided, monitor for lack of efficacy of these drugs.

12.3 Pharmacokinetics section

Model-informed approaches

Findings from a static mechanistic model-based analysis predicted that fexinidazole may significantly increase the systemic PK exposure (AUC) of sensitive CYP3A4 substrates and may decrease the systemic PK exposure of CYP2B6 substrates [see *Drug Interactions* (7.2)].

This model-based analysis predicted no significant drug interaction of fexinidazole with drugs that are substrates of CYP2C8, CYP2C9, or CYP2D6.

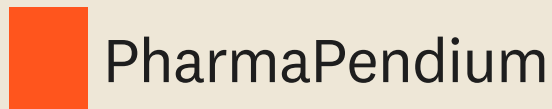
¹ EMA Approval: https://www.ema.europa.eu/documents/outside-eu-assessment-report/fexinidazole-winthrop-assessment-report_en.pdf

² FDA Approval: <https://www.accessdata.fda.gov/scripts/opdlisting/opd/detailedIndex.cfm?cfgridkey=513915>

³ FDA guidance: In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, January 2020. <https://www.fda.gov/media/134582/download>

⁴ https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214429s000lbl.pdf

⁵ FDA Prescribing information (US PI): https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214429s000lbl.pdf



PharmaPendium informs critical drug development decisions on safety and efficacy, risk assessments and mitigation, and study designs. It contains fully searchable FDA and EMA drug approval documents and FAERS data, a Drug-Drug Interaction Risk Calculator and comparative safety, pharmacokinetic, efficacy, and metabolizing enzyme and transporter data.

Acknowledgment

The PharmaPendium team and all of us at Elsevier would like to thank Sanofi/DNDi for sharing their story and congratulate them on their success in providing an easy-to-use medicine to help clinicians combat sleeping sickness.

For more information about PharmaPendium, visit elsevier.com/pharmapendium

