

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214429Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FEXINIDAZOLE TABLETS safely and effectively. See full prescribing information for FEXINIDAZOLE TABLETS.

FEXINIDAZOLE tablets, for oral use

Initial U.S. Approval: 2021

INDICATIONS AND USAGE

Fexinidazole Tablets is a nitroimidazole antimicrobial, indicated for the treatment of both first-stage (hemolymphatic) and second-stage (meningoencephalitic) human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* in patients 6 years of age and older and weighing at least 20 kg. (1)

Limitations of Use

Due to the decreased efficacy observed in patients with severe second stage HAT (cerebrospinal fluid white blood cell count (CSF-WBC) >100 cells/μL) due to *T. brucei gambiense* disease, Fexinidazole Tablets should only be used in these patients if there are no other available treatment options. (1, 5.1)

DOSAGE AND ADMINISTRATION

Administer Fexinidazole Tablets once daily with food each day at about the same time of the day. Do **not** break or crush tablets. (2.1, 2.2)

Recommended Dosage of Fexinidazole Tablets in Patients 6 years of age and older and weighing at least 20 kg (2.2)				
Body Weight	Type of Dose	Daily Dose	Number of Tablets	Duration of Treatment
Greater than or equal to 35 kg	Loading dose	1,800 mg	3	4 days
	Maintenance dose	1,200 mg	2	6 days
Greater than or equal to 20 kg to less than 35 kg	Loading dose	1,200 mg	2	4 days
	Maintenance dose	600 mg	1	6 days

DOSAGE FORMS AND STRENGTHS

Tablets: 600 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to fexinidazole, and/or nitroimidazole drugs (4)
- Patients with hepatic impairment (4)

WARNINGS AND PRECAUTIONS

- Decreased Efficacy in Severe Human African Trypanosomiasis caused by *Trypanosoma brucei gambiense*. (1, 5.1)

- QT Interval Prolongation** Prolongation of the QT interval due to Fexinidazole Tablets occurs in a concentration-dependent manner. Avoid use in patients with known prolongation, proarrhythmic conditions, and concomitant use with drugs that prolong the QT interval, those that block cardiac potassium channels, and/or those that induce bradycardia, or are inducers of hepatic CYP450. (5.2, 7.1, 7.2, 12.2)
- Neuropsychiatric Adverse Reactions** Adverse reactions such as agitation, anxiety, abnormal behavior, depression, suicidal ideation, nightmares, hallucination, and personality change have been observed during therapy. Inform patients and their caregivers of the risk. Consider alternative therapy or increased monitoring of the patient, including hospitalization in patients with psychiatric disorders, or if these adverse reactions occur. (5.3)
- Neutropenia** Avoid concomitant use of drugs which may cause neutropenia and monitor leukocyte count periodically. Monitor patients with neutropenia for symptoms or signs of infection. (5.4, 6.1)
- Potential for Hepatotoxicity** Evaluate liver-related laboratory tests at the start and during treatment. (4, 5.5)
- Risk of Disulfiram-like Reactions Due to Concomitant Use with Alcohol** Nitroimidazole-class drugs may cause a disulfiram-like reaction in patients who concurrently consume alcohol. Advise patients to avoid consumption of alcohol during treatment with and for at least 48 hours after completing therapy. (2.1, 5.6)
- Risk of Psychotic Reactions Due to Concomitant Use with Disulfiram** Psychotic reactions have been reported in patients concurrently taking disulfiram and nitroimidazole-class drugs. Avoid use in patients who have taken disulfiram within the last two weeks. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence >10%) are headache, vomiting, insomnia, nausea, asthenia, tremor, decreased appetite, dizziness, hypocalcemia, dyspepsia, back pain, upper abdominal pain, and hyperkalemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid use of herbal medicines and supplements. (7.1)
- See full prescribing information for complete list of clinically significant drug interactions. (7.2)

USE IN SPECIFIC POPULATIONS

- Avoid use in patients with severe renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fexinidazole Tablets are indicated for the treatment of both the first-stage (hemolymphatic) and second-stage (meningoencephalitic) human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* in patients 6 years of age and older and weighing at least 20 kg.

Limitations of Use

Due to the decreased efficacy observed in patients with severe second stage HAT (cerebrospinal fluid white blood cell count (CSF-WBC) >100 cells/ μ L) due to *T. brucei gambiense* disease, Fexinidazole Tablets should only be used in these patients if there are no other available treatment options [see *Warnings and Precautions* (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Patients should be closely followed by their healthcare provider during treatment with Fexinidazole Tablets.
- Fexinidazole Tablets must be administered with food [see *Dosage and Administration* (2.2)].
- Avoid consumption of alcoholic beverages during treatment with Fexinidazole Tablets and for at least 48 hours after completing therapy [see *Warnings and Precautions* (5.6)].
- If a first event of vomiting occurs after receiving Fexinidazole Tablets, **do not re-dose**. Administer the next dose the following day using the recommended treatment schedule [see *Adverse Reactions* (6.1)].
- If a scheduled dose is missed (not taken on the assigned day), normal dosing should resume the following day until the full course (10 days) of treatment has been completed. The clinical consequences of multiple missed doses of Fexinidazole Tablets are not known.

2.2 Recommended Dosage

Administer Fexinidazole Tablets, orally, once daily for a total of 10 days (loading dose plus maintenance dose) with food each day at about the same time of the day. Do **not** break or crush Fexinidazole Tablets.

The recommended dosage of Fexinidazole Tablets for patients 6 years of age and older is according to body weight as described in Table 1 below.

Table 1: Recommended Dosage of Fexinidazole Tablets in Patients 6 Years of Age and Older and Weighing at Least 20 kg

Body weight	Type of Dose	Recommended* Daily Dose	Number of 600 mg Fexinidazole Tablets Daily	Duration of Treatment
Greater than or equal to 35 kg	Loading dose	1,800 mg	3	4 days
	Maintenance dose	1,200 mg	2	6 days

Body weight	Type of Dose	Recommended* Daily Dose	Number of 600 mg Fexinidazole Tablets Daily	Duration of Treatment
Greater than or equal to 20 kg to less than 35 kg	Loading dose	1,200 mg	2	4 days
	Maintenance dose	600 mg	1	6 days

*Administer Fexinidazole Tablets once daily with food each day at about the same time of the day

3 DOSAGE FORMS AND STRENGTHS

Tablets: 600 mg of fexinidazole per tablet as pale-yellow, round, biconvex tablets debossed with “4512” on one side.

4 CONTRAINDICATIONS

Fexinidazole Tablets are contraindicated in:

- Patients with known hypersensitivity to Fexinidazole Tablets and/or any nitroimidazole-class drugs (e.g., metronidazole, tinidazole).
- Patients with hepatic impairment [see Warnings and Precautions (5.5), Adverse Reactions (6.1), and Use in Specific Populations (8.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Efficacy in Severe Human African Trypanosomiasis Caused by *Trypanosoma brucei gambiense*

Decreased efficacy was observed in patients treated with Fexinidazole Tablets as compared to nifurtimox-eflornithine combination therapy (NECT)-treated patients in a randomized, comparative open-label study in the subgroup of patients with severe second stage disease, as defined by cerebrospinal fluid white blood cell count (CSF-WBC) >100 cells/μL at baseline [see Clinical Studies (14)]. The 18-month success rate in this subgroup of patients with severe second stage disease was 86.9% with Fexinidazole Tablets compared to 98.7% with NECT with a difference of -11.8%, 95% confidence interval (CI) (-18.3%, -2.1%). All-cause mortality was higher in patients with severe disease treated with Fexinidazole Tablets than in patients treated with NECT through 24 months (7/160 [4.4%] vs 0/78 [0%], treatment difference 4.4%, 95% CI [-0.9%, 8.9%]).

Patients with severe second stage HAT (CSF-WBC >100 cells/μL) due to *T. brucei gambiense* disease should only be treated with Fexinidazole Tablets if there are no other available treatment options.

5.2 QT Interval Prolongation

Fexinidazole Tablets have been shown to prolong the QT interval in a concentration-dependent manner [see Clinical Pharmacology (12.2)]. Treatment with Fexinidazole Tablets caused an average increase of 19 msec in the QTcF interval. In clinical trials in HAT patients, three (<1%) patients in the fexinidazole group had a QTcF value of >500 ms versus none in the nifurtimox-eflornithine combination therapy (NECT) group.

Avoid use of Fexinidazole Tablets in patients who have:

- QTcF interval greater than 470 msec
- A history of torsade de pointes, congenital long QT syndrome, cardiac arrhythmias, uncompensated heart failure, or family history of sudden death
- Uncorrected hypokalemia

Avoid concomitant administration of Fexinidazole Tablets with other drugs that are known to prolong the QT interval, those that block cardiac potassium channels, and/or those that induce bradycardia [see *Drug Interactions* (7.1)].

Avoid concomitant administration of Fexinidazole Tablets with drugs that are inducers of hepatic CYP450 as these drugs may significantly increase plasma concentrations of fexinidazole's active metabolites: fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2). M2 plasma concentrations have been associated with increased QT prolongation risks [see *Drug Interactions* (7.2)].

If patients are, or need to be, treated with drugs known to prolong QTcF interval or to induce bradycardia either do not initiate therapy with Fexinidazole Tablets until such drugs are eliminated from the body (allow a washout period of 5 half-lives for such other drugs), or do not start such drugs until fexinidazole is eliminated from the body (allow a washout period of 7 days for Fexinidazole Tablets).

5.3 Neuropsychiatric Adverse Reactions

Adult patients treated with Fexinidazole Tablets reported a higher percentage of Central Nervous System (CNS) and psychiatric-related adverse reactions than those treated with nifurtimox eflornithine combination therapy (NECT) in a clinical trial [see *Adverse Reactions* (6.1)]. Increased incidence in insomnia, headache, and tremor was noted in the patients treated with Fexinidazole Tablets compared to NECT. In the same trial, adverse reactions representing mood changes and psychiatric disorders (such as agitation, anxiety, abnormal behavior, depression, nightmares, hallucination, and personality change) were more common in the patients treated with Fexinidazole Tablets compared to the NECT arm. Suicidal ideation has also been observed with Fexinidazole Tablets [see *Adverse Reactions* (6.1)]. Healthcare providers should inform patients and their caregivers of the risk for neuropsychiatric adverse reactions during treatment with Fexinidazole Tablets. In patients with current or a history of psychiatric disorders, or should such adverse reactions occur, healthcare providers should consider alternative therapy or increased monitoring of the patient, including hospitalization.

5.4 Neutropenia

Neutropenia (absolute neutrophil count less than 1,000 cells/mm³) has been reported in patients receiving Fexinidazole Tablets [see *Adverse Reactions* (6.1)]. In Trial 1, the adverse reaction occurred in patients with a baseline absolute neutrophil count of less than 5,000 cells/mm³. Avoid concomitant use of drugs which may cause neutropenia and monitor leukocyte count periodically. Carefully monitor patients with neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur.

5.5 Potential for Hepatotoxicity

Elevations in liver transaminases occurred in less than two percent of patients receiving Fexinidazole Tablets for the treatment of HAT [see *Adverse reactions* (6.1) and *Overdosage*].

(10)]. Evaluate liver-related laboratory tests at the start [see *Contraindications (4)*] and during treatment with Fexinidazole Tablets. Monitor patients who develop abnormal liver-related laboratory tests during treatment with Fexinidazole Tablets.

5.6 Risk of Disulfiram-like Reaction Due to Concomitant Use with Alcohol

Nitroimidazole-class drugs may cause a disulfiram-like reaction characterized by flushing, rash, weakness, abdominal cramps, nausea, vomiting and headache in patients who concurrently consume alcohol. Advise patients to avoid consumption of alcohol during treatment with Fexinidazole Tablets and for at least 48 hours after completing therapy [see *Dosage and Administration (2.1)*].

5.7 Risk of Psychotic Reactions Due to Concomitant Use with Disulfiram

Psychotic reactions have been reported in patients who were concurrently taking disulfiram and nitroimidazole drugs. Avoid use of Fexinidazole Tablets in patients who have taken disulfiram within the last two weeks.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse reactions are discussed in greater detail in other sections of labeling:

- Decreased Efficacy in Severe Human African Trypanosomiasis Caused by *Trypanosoma brucei gambiense* [see *Warnings and Precautions (5.1)*]
- QT Interval Prolongation [see *Warnings and Precautions (5.2)*]
- Neuropsychiatric Adverse Reactions [see *Warnings and Precautions (5.3)*]
- Neutropenia [see *Warnings and Precautions (5.4)*]
- Potential for Hepatotoxicity [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Fexinidazole Tablets were evaluated for the treatment of HAT due to *T. brucei gambiense* in three clinical trials, of which one was comparative and two were noncomparative. Trial 1 compared the safety of Fexinidazole Tablets to nifurtimox-eflornithine combination therapy (NECT) in second stage, meningoencephalitic HAT (N=394). Trial 2 enrolled patients with stage 1 hemolymphatic and early stage 2 HAT (N=230), and Trial 3 assessed the safety of fexinidazole in pediatric patients aged 6 years or older with any stage HAT (N=125).

The three trials were primarily conducted in the Democratic Republic of Congo (DRC) and a total of 749 patients received at least one dose of study medication. The patients ranged from 6 to 73 years of age, and 11 were more than 65 years old. Trials 1 and 3 enrolled more males than females (61% and 54% were males, respectively), while the gender distribution was equally balanced in Trial 2. The mean BMI ranged from 16.1 to 19.3 kg/m² across trials which was consistent with the nutritional status of the study population. Patients with AST/ALT >2 times

the upper limit of normal or total bilirubin >1.5 the upper limit of normal were excluded from the trials.

Trial 1 included 264 patients in the fexinidazole treatment arm and 130 patients in the NECT treatment arm. The patients were followed for up to 24 months from the completion of treatment.

Common Adverse Reactions

The most common adverse reactions occurring in >10% of HAT patients (15 years of age and older) receiving Fexinidazole Tablets in Trial 1 were headache, vomiting, insomnia, nausea, asthenia, tremor, decreased appetite, dizziness, hypocalcemia, dyspepsia, back pain, upper abdominal pain, and hyperkalemia.

Selected adverse reactions occurring in $\geq 2\%$ of HAT patients 15 years of age and older receiving Fexinidazole Tablets in Trial 1 are provided in Table 2.

Table 2: Selected Adverse Reactions Occurring in $\geq 2\%$ of HAT Patients 15 Years of Age and Older Receiving Fexinidazole Tablets in Trial 1

Adverse Reaction	Fexinidazole Tablets N=264 N (%)	NECT N=130 N (%)
Blood and lymphatic system disorders		
Neutropenia*	15 (5.7%)	4 (3.1%)
Cardiac disorders		
Palpitations	13 (4.9%)	5 (3.8%)
Eye disorders		
Photophobia	6 (2.3%)	0
Gastrointestinal disorders		
Vomiting	75 (28.4%)	37 (28.4%)
Nausea	68 (25.8%)	20 (15.4%)
Dyspepsia	34 (12.9%)	10 (7.7%)
Abdominal pain upper	27 (10.2%)	6 (4.6%)
Salivary hypersecretion	16 (6.1%)	3 (2.3%)
Constipation	13 (4.9%)	2 (1.5%)
Abdominal distension	8 (3.0%)	0
Gastritis	8 (3.0%)	2 (1.5%)
General disorders and administration site conditions		
Asthenia	60 (22.7%)	19 (14.6%)
Feeling hot	25 (9.5%)	3 (2.3%)
Chest pain	23 (8.7%)	5 (3.8%)
Gait disturbance	12 (4.5%)	2 (1.5%)
Metabolism and nutrition disorders		
Decreased appetite	56 (21.2%)	24 (18.5%)
Hypocalcemia	36 (13.6%)	3 (2.3%)
Hypoalbuminemia	23 (8.7%)	4 (3.1%)
Musculoskeletal and connective tissue disorders		

Adverse Reaction	Fexinidazole Tablets N=264 N (%)	NECT N=130 N (%)
Back pain	30 (11.4%)	12 (9.2%)
Neck pain	23 (8.7%)	7 (5.4%)
Muscle Spasms	7 (2.7%)	1 (0.8%)
Nervous system disorders		
Headache	92 (34.8%)	32 (24.6%)
Tremor	58 (22.0%)	15 (11.5%)
Dizziness	50 (18.9%)	18 (13.8%)
Extrapyramidal disorder	9 (3.4%)	2 (1.5%)
Paresthesia	6 (2.3%)	0
Psychiatric disorders		
Insomnia	74 (28.0%)	15 (11.5%)
Agitation	10 (3.8%)	1 (0.8%)
Anxiety	10 (3.8%)	0
Abnormal behavior	7 (2.7%)	1 (0.8%)
Respiratory, thoracic and mediastinal disorders		
Cough	16 (6.0%)	6 (4.6%)
Dyspnea	6 (2.3%)	1 (0.8%)
Skin and subcutaneous tissue disorders		
Pruritus	10 (3.8%)	4 (3.1%)
Hyperhidrosis	7 (2.7%)	2 (1.5%)
Vascular disorders		
Hot flush	13 (4.9%)	4 (3.1%)
Hypertension	12 (4.5%)	1 (0.8%)

* Defined as an absolute neutrophil count of less than 1,000 cells/mm³ occurring at any time following the first dose of study drug to the end of the study.

Other Adverse Reactions with Fexinidazole Tablets Occurring in Trial 1

The following adverse reactions were reported in less than 2% of patients aged 15 years and older with HAT, treated with Fexinidazole Tablets in Trial 1:

Psychiatric Disorders: hallucinations, psychotic disorder, depression, personality change, suicidal ideation

Laboratory Investigations: elevations of liver transaminases [see *Warnings and Precautions (5.5)*] and *Overdosage (10)*]

The safety profile of Fexinidazole Tablets in Trials 2 and 3, including in pediatric subjects aged 6-15 years old, was similar to that of Trial 1 [see *Use in Specific Populations (8.4)*].

Specific Adverse Reactions

Vomiting

In the clinical trials, the incidence of vomiting within 30 minutes of administration of Fexinidazole Tablets was higher in pediatric patients (20%) than in adult patients (6.1%). There was a trend of increased incidence of vomiting during the loading phase. Generally, vomiting did not lead to treatment discontinuation.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions

Herbal Medicines and Supplements

There is a potential for pharmacodynamic interactions and/or toxicities between fexinidazole and herbal medicines and supplements. Avoid concomitant use of herbal medicines and supplements during treatment with Fexinidazole Tablets.

Drugs that May Prolong the QT Interval and/or Induce Bradycardia

Coadministration of Fexinidazole Tablets with drugs known to block potassium channels (e.g., antiarrhythmics, neuroleptics, fluoroquinolones, imidazole and triazole antifungals, pentamidine) prolong the QT interval (e.g., antimalarials, phenothiazines, tricyclic antidepressants, terfenadine and astemizole, IV erythromycin, and quinolone antibacterial drugs) and/or induce bradycardia (such as β -blockers) should be avoided [see *Warnings and Precautions* (5.2)].

7.2 Pharmacokinetic 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.
Drugs Substrates of OCT2, OAT1, OAT3, MATE1, and MATE2-K Transporters	
<i>Examples (not fully inclusive):</i>	Metformin, dofetilide, adefovir, cefaclor, furosemide

<i>Clinical Impact</i>	Increased risk for adverse reactions associated with increased concentrations of the drug due to inhibition of these transporters by fexinidazole [see <i>Clinical Pharmacology (12.3)</i>].
<i>Prevention or Management</i>	Avoid concomitant use with Fexinidazole Tablets. If coadministration cannot be avoided, monitor for adverse reactions associated with these drugs.

Table 4: Effect of other Drugs on Fexinidazole

CYP450 Inducers	
<i>Examples (not fully inclusive):</i>	Rifampin, phenytoin, St. John's wort, carbamazepine
<i>Clinical Impact</i>	Increased risk for adverse reactions associated with increased systemic exposure to the M1 and M2 metabolites of fexinidazole. M2 plasma concentrations have been associated with the increased risk of QT interval prolongation.
<i>Prevention or Management</i>	Avoid concomitant use with Fexinidazole Tablets [see <i>Warnings and Precautions (5.2)</i> and <i>Clinical Pharmacology (12.3)</i>].
CYP450 Inhibitors	
<i>Examples (not fully inclusive):</i>	Clarithromycin, itraconazole, voriconazole, erythromycin, fluconazole
<i>Clinical Impact</i>	Multiple CYP450 enzymes are involved in the metabolism of fexinidazole to its pharmacologically active M1 and M2 metabolites. Although no clinical drug interaction studies were performed with CYP450 inhibitors, the formation of the M1 and M2 metabolites may be decreased.
<i>Prevention or Management</i>	Avoid concomitant use with Fexinidazole Tablets. If coadministration cannot be avoided, monitor for lack of efficacy of fexinidazole due to potential for decreased plasma concentrations of the M1 and M2 metabolites [see <i>Clinical Pharmacology (12.3)</i>].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are risks to the mother and fetus associated with untreated HAT due to *T. brucei gambiense* during pregnancy (see *Clinical Considerations*). Available data from clinical trials with fexinidazole use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects or miscarriage.

There were no effects on prenatal development in embryo-fetal studies where pregnant rats were administered oral fexinidazole during organogenesis at a dose similar to the clinical dose based on AUC comparisons. Effects of fexinidazole on embryo-fetal development were observed in the rat and in the rabbit at doses harmful to the dams only. Exposure of fexinidazole and its metabolites at those maternal toxic doses in rats and rabbits were 2 times and less than 0.02 times the clinical exposure, respectively. In the prenatal and postnatal development study, administration of oral fexinidazole to pregnant rats during organogenesis and through lactation resulted in lower body weights in first generation offspring from dams treated at approximately 1.03 times the clinical exposure based on AUC comparisons.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal Risk

There are adverse effects on maternal and fetal outcomes associated with untreated HAT due to *T. brucei gambiense* in pregnancy. Disease progression may occur during pregnancy. Pregnant women should be treated for HAT due to *T. brucei gambiense* during pregnancy to prevent vertical transmission. For timing of treatment during pregnancy, consider the benefits of Fexinidazole Tablets to the mother and the potential risks to the fetus.

Data

Animal data

In the embryo-fetal toxicity studies, pregnant rats were exposed from gestation day (GD) 6 through GD 17. There was no effect on prenatal development in the rat up to the daily dose of 200 mg/kg, similar to the clinical dose based on AUC comparisons.

Maternal toxicity was evidenced by the significantly reduced body weight gain observed at 800 mg/kg. Delayed ossification (sternbrae, metacarpals and caudal vertebrae) and reduced fetal and placental weights were observed in the presence of maternal toxicity.

In the rabbit embryo-fetal development study, pregnant rabbits were exposed from GD 6 to GD 20. Fexinidazole resulted in abortions in the presence of maternal toxicity (reduced food consumption and reduced body weight gain) at doses of 20 mg/kg/day and above, less than 0.02 times the clinical exposures, based on pharmacokinetics comparisons.

In the prenatal and postnatal development study, female rats were exposed from GD 6 to lactation day 21. Lower body weights were reported in F1 pups from dams treated (approximately 1.03 times the clinical exposure based on AUC comparisons) throughout lactation. Sexual maturity showed a minimal delay for both males and females. Postweaning development for behavior and reproductive performance did not indicate any late adverse effect on the progeny.

8.2 Lactation

Risk Summary

There are no data on the presence of fexinidazole in human milk or the effect on milk production. There are no reports of adverse effects to the breastfed child associated with fexinidazole exposure through breastmilk based on a limited number of reported cases. Fexinidazole is present in rat milk (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fexinidazole Tablets and any potential adverse effects on the breastfed child from fexinidazole or from the underlying maternal condition.

Data

In lactating rats given a single oral dose of 800 mg/kg ¹⁴C-fexinidazole, fexinidazole and/or related metabolites were detected in the milk.

8.4 Pediatric Use

The safety and effectiveness of Fexinidazole Tablets for the treatment of both the first-stage (hemolymphatic) and second-stage (meningoencephalitic) HAT due to *Trypanosoma brucei gambiense* have been established in pediatric patients aged 6 years and older and weighing at least 20 kg. Use of Fexinidazole Tablets for this indication is supported by evidence from an adequate and well-controlled trial in adults with additional efficacy, pharmacokinetic and safety data in pediatric patients aged 6 years and older [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14)].

Pediatric patients may be more sensitive to vomiting. The safety profile for Fexinidazole Tablets in pediatric patients was generally similar to that of adult patients with the exception of more frequent vomiting within 2 hours of administration of Fexinidazole Tablets. Vomiting did not result in permanent treatment discontinuation [see *Adverse Reactions* (6.1)].

The safety and efficacy of Fexinidazole Tablets have not been established in pediatric patients younger than 6 years old and/or less than 20 kg in body weight.

8.5 Geriatric Use

Of the 619 subjects in the three clinical trials treated with Fexinidazole Tablets for HAT, there were 11 subjects who were 65 years of age or older, and no subjects greater than 75 years of age. There were an insufficient number of elderly subjects to detect differences in safety and/or effectiveness between elderly and younger adult patients.

8.6 Renal Impairment

No dosage adjustment is needed for patients with mild to moderate renal impairment with estimated glomerular filtration rates (eGFR) from 30 mL/min/1.73 m² to less than or equal to 89 mL/min/1.73 m² [see *Clinical Pharmacology* (12.3)]. The pharmacokinetics of fexinidazole in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) is unknown. Avoid the use of Fexinidazole Tablets in patients with severe renal impairment.

8.7 Hepatic Impairment

The pharmacokinetics of fexinidazole in patients with hepatic impairment is unknown. Since fexinidazole is extensively metabolized by the liver, Fexinidazole Tablets are contraindicated in patients with hepatic impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.5)].

10 OVERDOSAGE

Randomized, controlled clinical studies were conducted in normal adult male volunteers who were administered single or multiple oral doses of fexinidazole of up to 3,600 mg daily for 14 days (not an approved dose). The subjects experienced adverse reactions of increased transaminases, vomiting and panic attack [see *Adverse Reactions* (6.1)].

Reported symptoms of overdosage in a pediatric HAT patient following ingestion of a higher than recommended dosing regimen in Trial 3 included vomiting over the first 5 days of treatment and increased potassium and decreased calcium levels from Day 11 to Week 9.

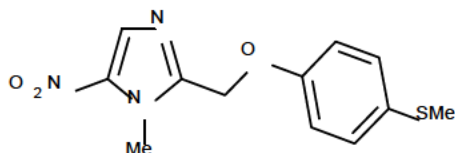
There is no specific antidote for Fexinidazole Tablets. Treatment should be supportive with appropriate monitoring.

11 DESCRIPTION

Fexinidazole Tablets contain fexinidazole, a nitroimidazole antimicrobial drug for oral use.

The chemical name of fexinidazole is 1-methyl-2-{{[4-(methylthio) phenoxy] methyl}-5-nitro-1H-imidazole.

Its molecular formula is $C_{12}H_{13}N_3O_3S$ and the molecular weight is 279.3 g/mol. The structural formula is:



Fexinidazole is a yellow powder. It is practically insoluble in water, sparingly soluble in acetone and acetonitrile, very slightly soluble in ethanol and slightly soluble in methanol.

Fexinidazole 600 mg tablets contain the active ingredient fexinidazole and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fexinidazole is an antiprotozoal drug [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

Cardiac Electrophysiology

Concentration-dependent QTcF prolongation was observed with administration of Fexinidazole Tablets. Based on the exposure-response relationship, the mean (upper 90% confidence interval) increase in QTcF is predicted to be 19.0 msec (23.3 msec) at the recommended dosing regimen. The observed increase in QTcF appears to be associated with the M2 (sulfone) metabolite of fexinidazole [see *Warning and Precautions* (5.2)].

12.3 Pharmacokinetics

The pharmacokinetics (PK) of fexinidazole and its two pharmacologically active M1 (sulfoxide) and M2 (sulfone) metabolites following administration of the recommended adult dosage regimen of Fexinidazole Tablets in 12 healthy adult male subjects under fed conditions are presented in Table 5.

Table 5: Pharmacokinetics of Fexinidazole and its Active M1 and M2 Metabolites following Administration of Fexinidazole Tablets 1,800 mg Once Daily for 4 Days, Then 1,200 mg Once Daily for 6 Days to Healthy Adult Subjects Under Fed Conditions (N=12)

		Fexinidazole	M1	M2
Mean (±SD) C _{max} mcg/mL	Day 1	1.6 (±0.4)	8.1 (±2.2)	7.5 (±3.3)
	Day 4	0.8 (±0.3)	8.0 (±2.3)	19.6 (±5.4)
	Day 10	0.5 (±0.2)	5.9 (±2.1)	12.5 (±3.5)
Mean (±SD) AUC _(0-24 hours) mcg·h/mL	Day 1	14.3 (±2.6)	102.3 (±28.5)	110.1 (±41.1)
	Day 4	11.6 (±2.2)	127.9 (±49.2)	391.5 (±126.7)
	Day 10	7.0 (±2.5)	84.2 (±36.3)	252.4 (±73.6)
Absorption				
Median T _{max} (Range) on Day 4, hours		4 (0-9)	4 (0-6)	6 (0-24)
Effect of Food*		The AUC of fexinidazole, M1, and M2 were approximately 4 to 5-fold higher following administration with food compared to the fasted state.		
Distribution				
Apparent Volume of Distribution on Day 4, L		3222 (±1199)	NA	NA
Plasma Protein Binding		98%	41%	57%
Mean (Range) CSF concentrations at 24 hours after the last fexinidazole dose on Day 10, mcg/mL [†]		NA	1.39 (0-4.5)	6.45 (0.3-14.9)
Mean (Range) CSF to DBS Ratios [†]		NA	0.53 (0.1-2.2)	0.36 (0.1-0.8)
Elimination				
Mean (±SD) Day 10 Half-life, hours		15 (±6)	16 (±6)	23 (±4)
Mean (±SD) Apparent Clearance on Day 4, L/hour		161 (±37)	NA	NA
Metabolism				
Fexinidazole		• Fexinidazole is metabolized to M1 by several CYP450 enzymes, including CYP3A4 and flavin monooxygenases.		
Active Metabolites		• Several CYP450 enzymes including, CYP3A4 and flavin monooxygenases, are involved in the metabolism of M1 to M2. • M2 is not further metabolized. • The AUC ₀₋₂₄ of M1 and M2 are 11 and 34-fold higher, respectively, than that of fexinidazole.		
Excretion				
Urine		Less than 3.2% of a given dose of Fexinidazole Tablets, primarily as M1 and M2 metabolites		

$C_{\max}$ = maximum plasma concentration; $T_{\max}$ = time to maximum concentration; CSF = cerebrospinal fluid; CYP = cytochrome P450 enzymes; $AUC_{0-24 \text{ hours}}$ = area under the plasma concentration-time curve from time zero to 24 hours, AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last timepoint with measurable analyte concentrations; DBS = dried blood spot

NA: Not available or not applicable

* The effect of food following administration of a single 1,200 mg dose with a meal containing approximately 963 Kcal with 62% of total calories from fat, 17% from protein, and 21% from carbohydrate (n=12).

[†] From study in patient with HAT.

Specific Populations

Elderly patients

No specific pharmacokinetic studies have been performed in patients older than 65 years of age. In a population PK analysis of patients with HAT over a range of ages from 6 to 71 years, age was not a significant covariate affecting the PK of fexinidazole and the M1 and M2 metabolites and no differences in the PK of any of these three moieties were observed.

Pediatric patients

The ranges of plasma AUC values of fexinidazole, M1, and M2 in pediatric and adult HAT patients with body weights greater than or equal to 20 kg were overlapping following administration of Fexinidazole Tablets at the recommended pediatric and adult dosage regimens, indicating similar systemic exposures across body weights of 20 kg and greater.

Hepatic impairment

No specific PK studies were conducted in patients with hepatic impairment. Furthermore, insufficient data were available to assess the effect of hepatic impairment on fexinidazole PK from the clinical trials [see *Use in Specific Populations (8.7)*].

Renal Impairment

A population PK analysis, based on baseline renal function, was carried out with data from 317 HAT patients enrolled in clinical trials that included 212 patients with normal renal function (eGFR greater than or equal to 90 mL/min/1.73 m²), 89 patients with mild renal impairment (eGFR 60 to less than 90 mL/min/1.73 m²), and 14 patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²). The predicted AUC₀₋₂₄ estimates for fexinidazole and its M1 and M2 metabolites were similar in patients with mild or moderate renal impairment compared to those patients without renal impairment. The PK of fexinidazole in patients with severe renal impairment has not been studied [see *Use in Specific Populations (8.6)*].

Race/ethnicity

Insufficient data were available from the clinical trials to assess the effect of race or ethnicity on fexinidazole PK.

Drug Interaction Studies

In vitro studies

Cytochrome P450 (CYP450) Enzymes: Fexinidazole has the potential to inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4/5; M1 has the potential to inhibit CYP2C19; M2 does not inhibit any CYPs.

Fexinidazole, M1, or M2 do not induce CYP3A4; fexinidazole and M1 have the potential to induce CYP1A2 and CYP2B6 [see *Drug Interactions (7.2)*].

Transporter Systems: Fexinidazole inhibits OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2-K transporters. M1 inhibits OAT3, MATE1, and MATE2-K. M2 inhibits OCT2, OAT1, OAT3, MATE1, and MATE2-K. Coadministration with Fexinidazole Tablets may increase the plasma concentrations of drugs that are substrates of these aforementioned transporters [see *Drug Interactions (7.2)*]. Fexinidazole, M1, or M2 do not inhibit P-gp or BCRP.

Clinical studies

A clinical drug-drug interaction study evaluated the effect of fexinidazole following administration of 1,800 mg Fexinidazole Tablets for four days, followed by 1,200 mg on Day 5, with single dose administration of 100 mg caffeine (probe substrate of CYP1A2) and 20 mg omeprazole (probe substrate of CYP2C19) on Day 4 in healthy subjects. The mean caffeine AUC was 2-fold higher, with no significant increase in $C_{\max}$ compared to when caffeine was administered alone. The mean $C_{\max}$ and AUC of omeprazole were approximately 2-fold higher compared to when omeprazole was administered alone [see *Drug Interactions (7.2)*].

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.

12.4 Microbiology

Mechanism of Action

Studies with *Trypanosoma brucei* and other protozoans suggest that, like for other nitro-containing drugs, the nitroreductase (NTR) enzyme plays an important role in the bioactivation of fexinidazole resulting in generation of reactive amines and damage to DNA and proteins. The activity of fexinidazole and its metabolites (M1 and M2) is trypanocidal and appears to be concentration and time dependent. However, the precise mechanism by which fexinidazole and the two metabolites exhibit activity against *T. brucei* is not known.

Antimicrobial Activity

Fexinidazole and its two metabolites, M1 and M2, are active against the trypanosomes of *Trypanosoma brucei gambiense*.

Resistance

In vitro studies suggest a potential for development of resistance in *T. brucei* against fexinidazole.

The mechanism of resistance appears to be similar to other nitro-containing drugs, such as nifurtimox, and include down-regulation of Type 1 NTR. However, the clinical relevance of these findings is not known.

Cross-Resistance

Nonclinical studies suggest cross-resistance between fexinidazole and other nitro-containing drugs such as nifurtimox. This appears to be due to down regulation of Type I NTR. Although the clinical relevance of these findings is not known, the potential for the development of resistance to fexinidazole in patients previously treated with nifurtimox-eflornithine combination therapy (NECT) cannot be discounted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

No carcinogenicity study was performed with fexinidazole.

Carcinogenicity has been observed in mice and rats treated chronically with nitroimidazole-class drugs which are structurally similar to fexinidazole. It is unclear if the findings of tumors in lifetime rodent studies indicate a risk to patients taking a 10-day treatment of Fexinidazole Tablets for HAT.

Mutagenesis

Fexinidazole and the M2 metabolite were mutagenic in the Ames test. Fexinidazole was negative in the *in vitro* micronucleus test in cultured human peripheral blood lymphocytes, the rat liver unscheduled DNA synthesis (UDS) assay, and the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In the fertility and early embryonic development study, male rats were treated for 28 days prior to start of cohabitation with treated females and throughout the cohabitation period until sacrifice. Female rats were treated for 14 days prior to start of cohabitation with treated males throughout the cohabitation period until copulation occurred and up to GD 7. Fexinidazole showed no effect on fertility parameters and no evidence of impairment of reproductive performance up to the dose of 600 mg/kg/day (estimated to be approximately 1.03 times the clinical exposure based on AUC comparisons).

14 CLINICAL STUDIES

Trial 1

The efficacy and safety of Fexinidazole Tablets were evaluated in a randomized, comparative open-label trial (Trial 1, NCT01685827) conducted in adult patients with late second-stage HAT due to *T. brucei gambiense*. Patients had evidence of parasites in blood, lymph and/or cerebrospinal fluid (CSF) at trial enrollment. If testing for parasites in CSF was negative, a CSF WBC >20 cells/μL was required to confirm late second-stage HAT. Patients (n=394) were randomized in a 2:1 ratio to a 10-day treatment regimen of either Fexinidazole Tablets (n=264) or nifurtimox-eflornithine combination therapy (NECT) (n=130). The mean age was 35 years (range 15 to 71) and 61% were male. The fexinidazole tablet group received 1,800 mg of Fexinidazole Tablets orally once daily on Days 1 through 4, followed by 1,200 mg orally once daily on Days 5 through 10, with all dosing in the fed state. The NECT control arm received nifurtimox tablets 15 mg/kg/day in three divided doses for 10 days as well as eflornithine injectable solution 400 mg/kg/day in two divided doses for 7 days. Patients were hospitalized throughout their treatment and were allowed to leave the hospital from Day 13 onwards if their clinical status was satisfactory. Patients were followed up at 3, 6, 12, 18, and 24 months after the end of treatment visit. HAT symptoms reported at baseline in >50% of patients included headache, pruritus, sleepiness, weight loss, and asthenia. The median CSF WBC count was 157 cells/μL.

The outcome at 18 months was considered a success if patients were classified as a cure or probable cure as defined below:

- Cure: Patient is alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20 cells/ μ L.
- Probable cure for patients who refused a lumbar puncture (or who had a hemorrhagic CSF sample) at 18 months: No parasites in the blood or lymph and a satisfactory clinical condition without clinical signs or symptoms (or clinical status is unlikely to be due to HAT), CSF WBC < 50 cells/ μ L at 6 and/or 12 months and not increasing at 12 months, as long as there was no indication of a relapse up to 24 months and no definitive failure (presence of trypanosomes) had been observed before in any body fluid.

Success rates at 18 months are shown in Table 6 for the modified intention-to-treat (mITT) population, which consisted of all randomized patients who received at least one dose of study treatment but excluded 5 randomized patients due to geopolitical unrest. The success rate in the fexinidazole treatment arm was lower than in the NECT arm. Additionally, more deaths occurred in the fexinidazole treatment arm at 24 months ($n=9$, 3.4%) compared to the NECT treatment arm ($n=2$, 1.6%). This decreased efficacy and increased mortality was noted in the subgroup of patients who had CSF-WBC > 100 cells/ μ L at baseline [see *Warnings and Precautions (5.1)*]. The results at 24 months were consistent with the results at 18 months with 24-month success rates of 89.7% (235/262) in the fexinidazole treatment arm and 97.6% (124/127) in the NECT arm.

Table 6: Success Rates at 18 Months (mITT population) in Trial 1

	Fexinidazole	NECT	Difference (97% CI*)
N	262	127	–
Success at 18 months [†]	239 (91.2%)	124 (97.6%)	-6.4% (-11.6%, -0.1%)
Success at 18 months by baseline CSF-WBC [‡]			
Baseline CSF-WBC ≤ 100 cells/ μ L	100/102 (98.0%)	47/49 (95.9%)	–
Baseline CSF-WBC > 100 cells/ μ L	139/160 (86.9%)	77/78 (98.7%)	–

* Analysis adjusted for interim analysis to control the overall Type I error at two-sided 0.05.

[†] Two fexinidazole treated patients were considered as failures due to loss to follow-up and consent withdrawal prior to 18 months.

[‡] CSF-WBC represents white blood cell count in cerebrospinal fluid at baseline.

Trial 2 and Trial 3

Additional supportive evidence for efficacy in early stage HAT due to *T. brucei gambiense*, and in pediatric patients was obtained from two single-arm trials: a single-arm trial in adults (Trial 2, NCT02169557), and a single-arm trial in pediatric patients aged 6 to 15 years old and weighing at least 20 kg (Trial 3, NCT02184689). In Trial 2, the mean age of patients was 34 years and 82% of patients had evidence of first-stage HAT (evidence of trypanosomes in the blood or lymph, no trypanosomes in the CSF, and CSF WBC ≤ 5 cells/ μ L). In Trial 3, the mean age of patients was 11 years and 55% of patients had evidence of first-stage HAT. Fexinidazole Tablets 1,200 mg, was given in fed condition once a day on Days 1 through 4, followed by 600 mg on Days 5 through 10 to patients weighing < 35 kg, and all other patients received the adult dosing regimen. Treatment success proportions in all patients with first- or late-stage HAT were 98.7% (227/230, 95% CI [96.2%, 99.7%]) at 12 months in Trial 2 and 97.6% (122/125, 95% CI [93.1%, 99.5%]) at 12 months in Trial 3. The results at 18 months were consistent with the results at 12 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fexinidazole 600 mg tablets are pale-yellow, round, biconvex tablets debossed with "4512" on one side.

Fexinidazole 600 mg tablets are supplied as:

- NDC 0024-4512-24, child-resistant blister pack of 24 tablets (10-day dose pack) for adults and pediatric patients weighing 35 kg or more.
- NDC 0024-4512-14, child-resistant blister pack of 14 tablets (10-day dose pack) for pediatric patients older than 6 years weighing 20 kg to less than 35 kg.

Store below 30°C (86°F). Store in the original package in order to protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Administration with Food

Advise the patient that Fexinidazole Tablets must be taken with food each day at about the same time of the day (e.g., during or immediately after the main meal of the day), to make sure it is adequately absorbed [see *Dosage and Administration* (2.1, 2.2)].

Alcohol Consumption

Advise patients not to consume alcoholic beverages during treatment with Fexinidazole Tablets and for at least 48 hours after completing Fexinidazole Tablets therapy [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.6)].

Vomiting

Advise the patient **not** to administer an additional dose if vomiting occurs after the administration of Fexinidazole Tablets but continue with the next scheduled dose the following day. If a second event of vomiting occurs after administration of any other dose of Fexinidazole Tablets, counsel the patient on the importance of contacting the healthcare provider immediately [see *Dosage and Administration* (2.1)].

Missed Doses

Advise patients that if a scheduled dose is missed (not taken on the assigned day), normal dosing should resume the following day until the full course (10 days) of treatment has been completed. Counsel the patient on the importance of contacting the health care practitioner immediately if a second scheduled dose is missed [see *Dosage and Administration* (2.1)].

Neuropsychiatric Adverse Reactions

Counsel patients and their caregivers of the risk for neuropsychiatric adverse reactions, such as insomnia, headache, tremor, mood changes, psychiatric disorders (such as agitation, anxiety, abnormal behavior, depression, nightmares, hallucination, and personality change) and suicidal ideation [see *Warnings and Precautions* (5.3) and *Adverse Reactions* (6.1)]. If such adverse reactions occur, advise the patients and their caregivers to contact their healthcare provider immediately.

Dizziness

Counsel the patient that they should not drive or use machines if they feel tired or dizzy. Dizziness, fatigue, asthenia, and somnolence have been reported following treatment with Fexinidazole Tablets [see *Adverse Reactions (6.1)*].

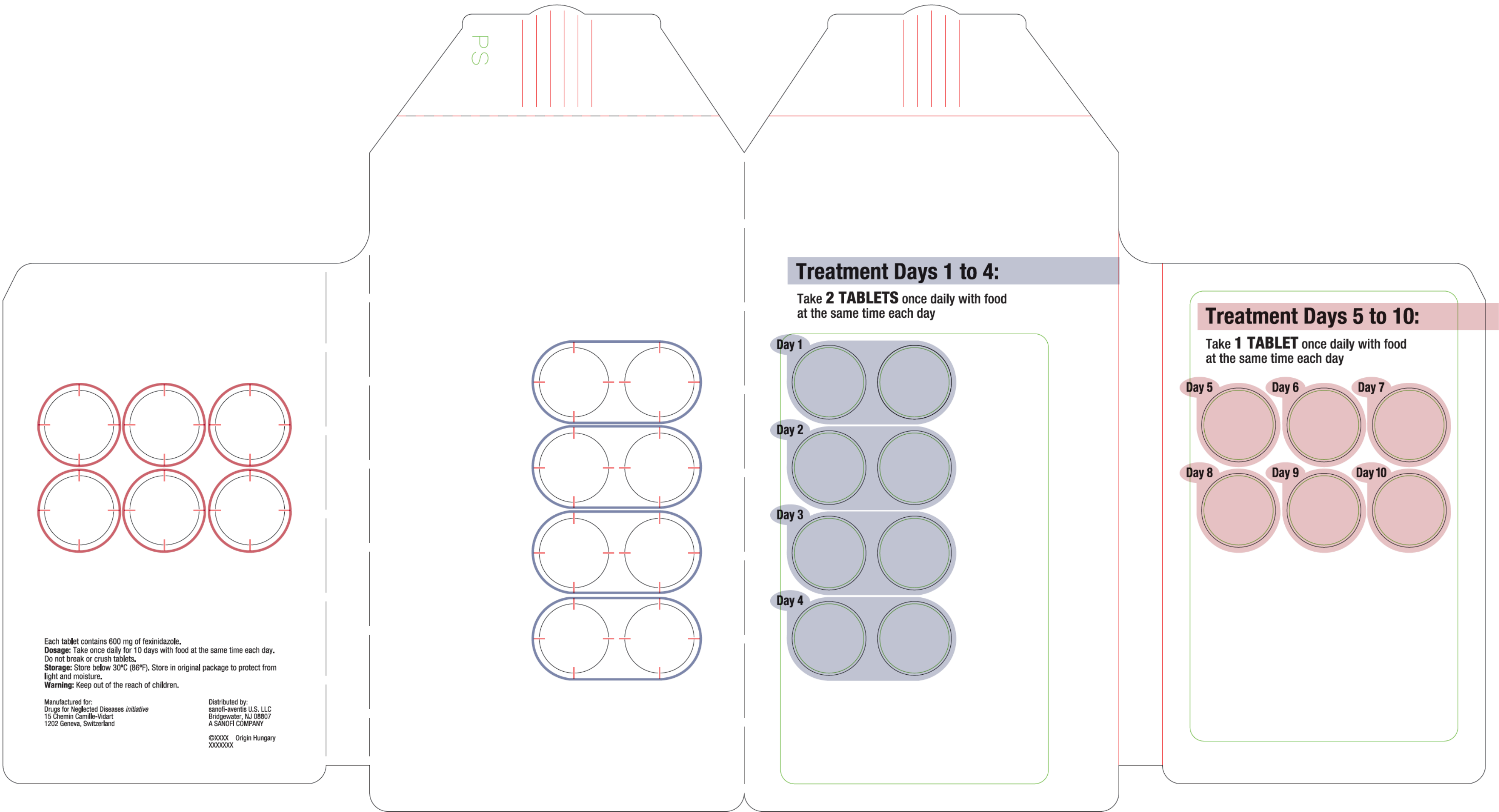
Drug Interactions

Advise patients to disclose to their healthcare provider all other medications, including herbal medicines, the patient is currently taking while being treated with fexinidazole tablets [see *Drug Interactions (7)*].

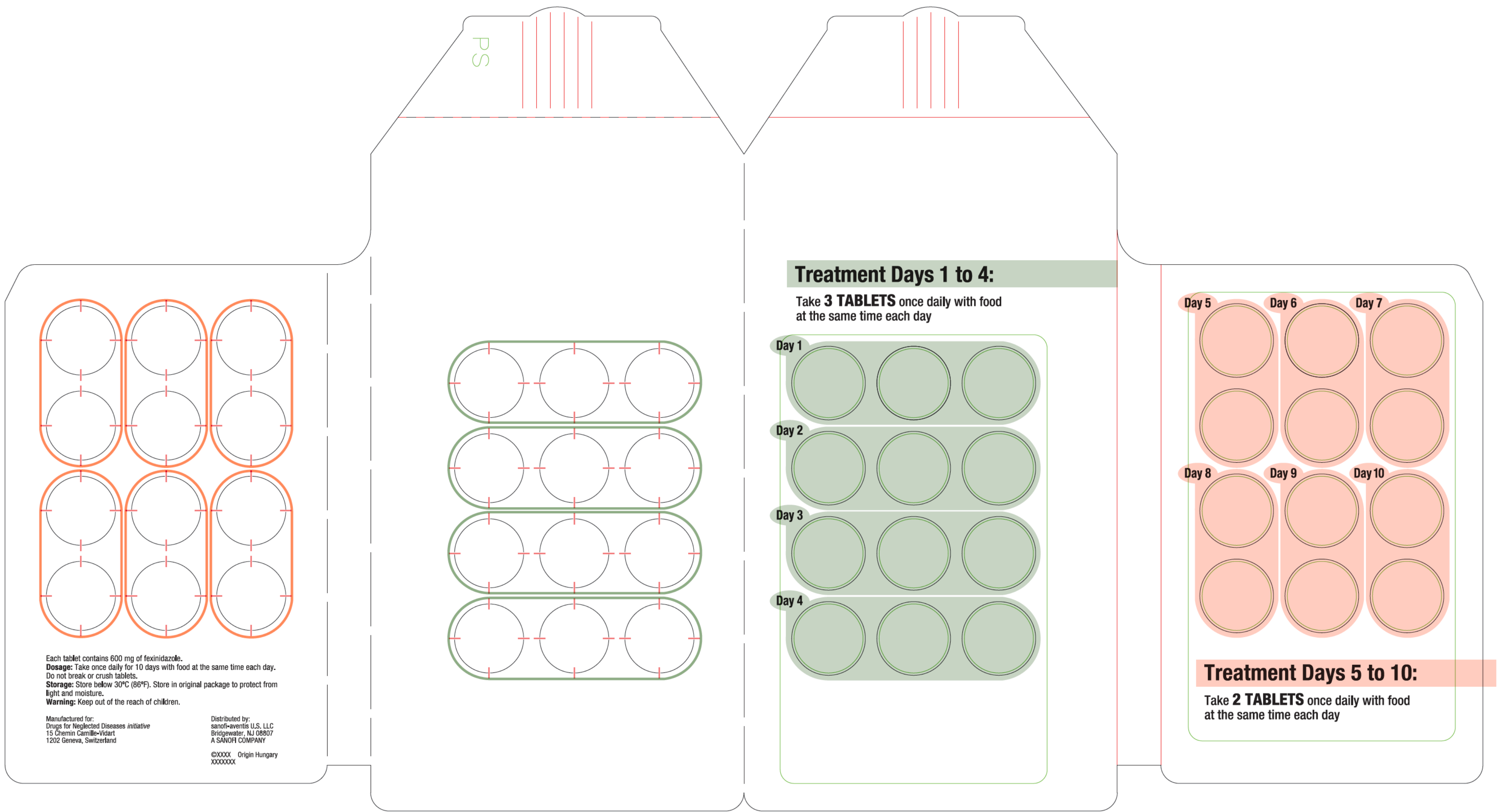
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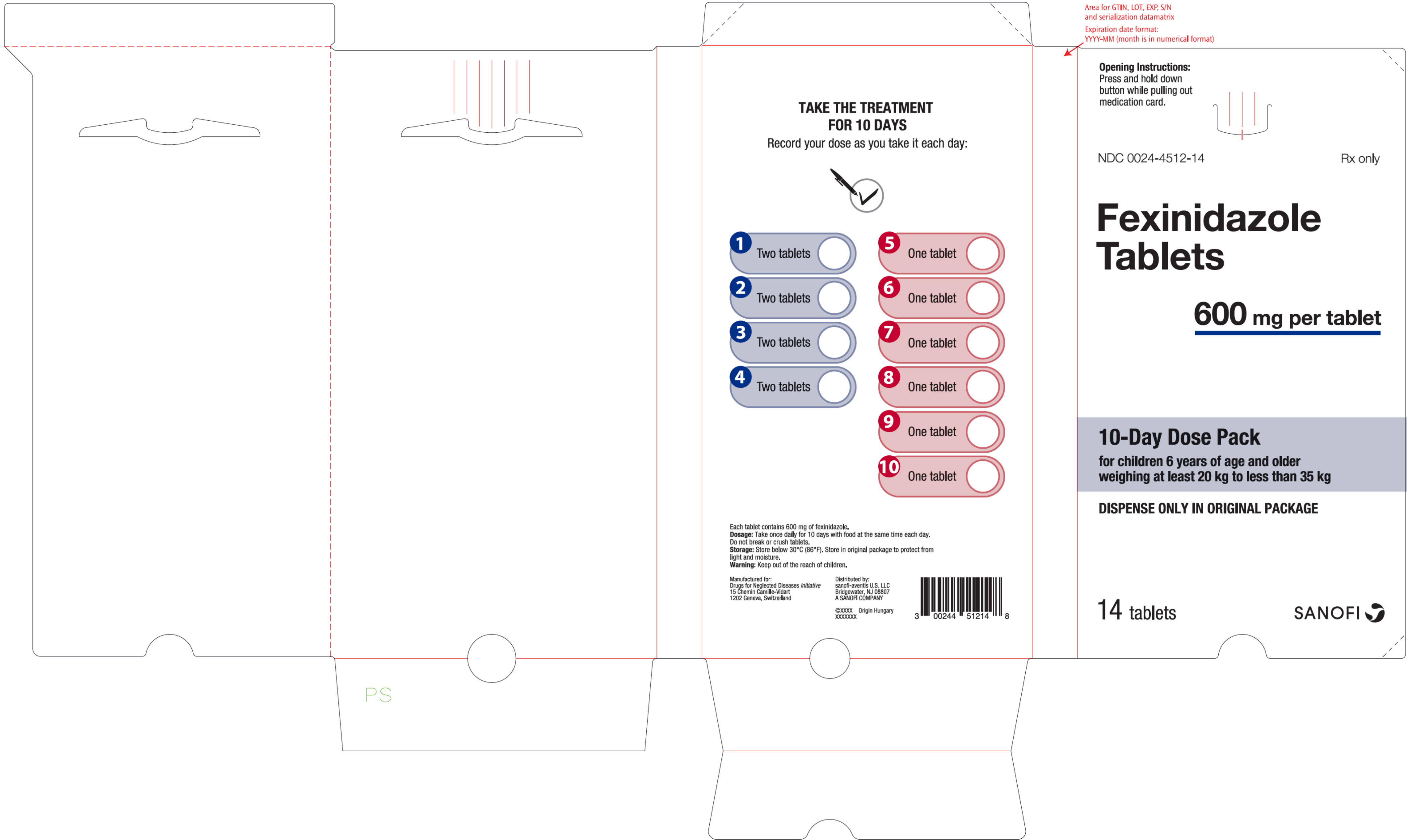
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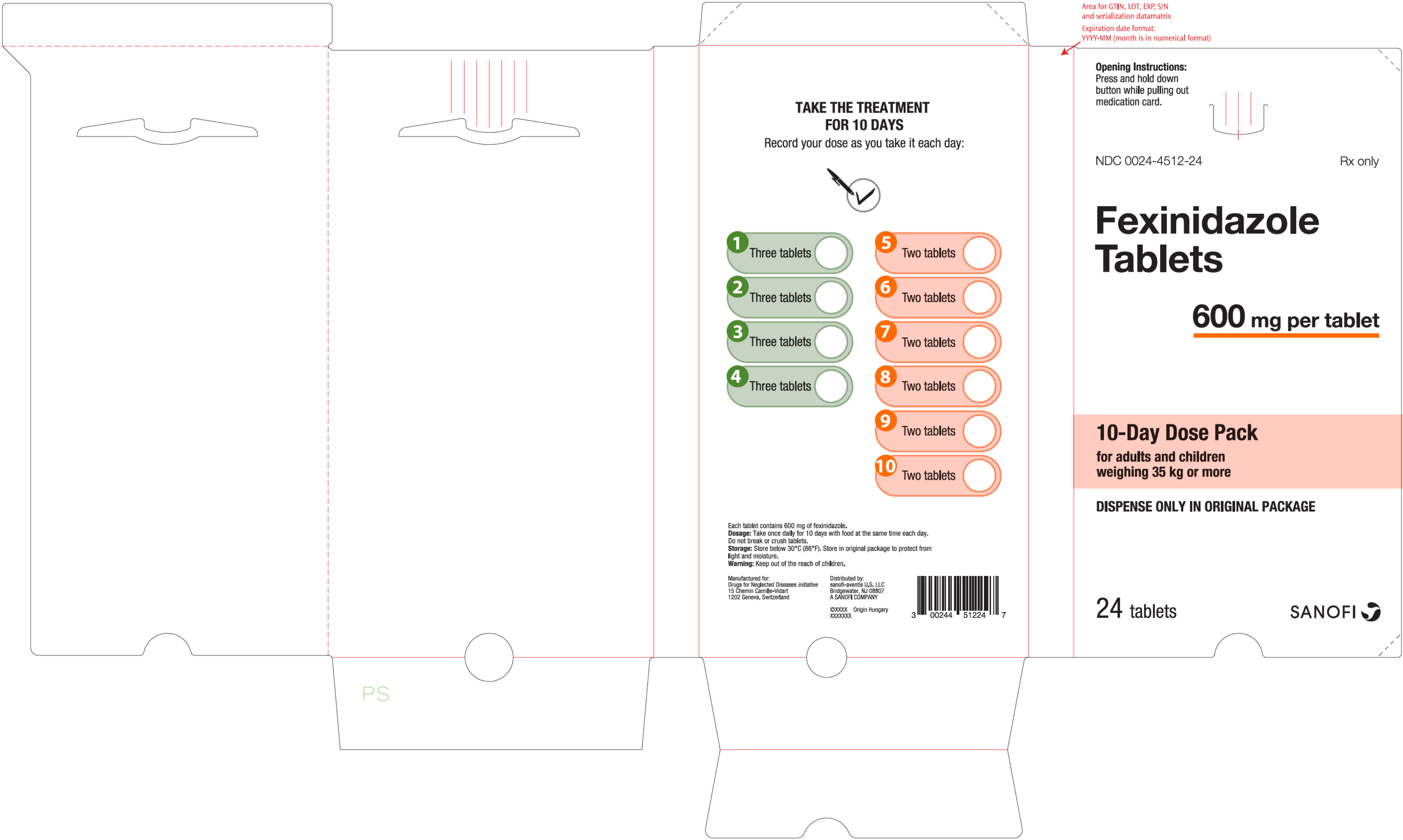
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