AHFS®*first*Release™

AHFS® Drug Information™

Nifurtimox

Nifurtimox is a nitrofuran antiprotozoal.

Class: 8:30.92 • Antiprotozoals, Miscellaneous (AHFS primary)

Brands: Lampit®

Uses

Nifurtimox has the following uses:

- Nifurtimox is an antiprotozoal, indicated in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas disease (American trypanosomiasis), caused by *Trypanosoma cruzi*. This indication is approved under accelerated approval based on the number of treated patients who became immunoglobulin G (IgG) antibody negative or who showed an at least 20% decrease in optical density on two different IgG antibody tests against antigens of *T. cruzi*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Dosage and Administration

General. Nifurtimox is available in the following dosage form(s) and strength(s):

- Tablets: 30 mg (functionally scored)
- Tablets: 120 mg (functionally scored)

Dosage. It is *essential* that the manufacturer's labeling be consulted for more detailed information on dosage and administration of this drug. Dosage summary:

Pediatric Patients.

Dosage and Administration.

- Nifurtimox tablets must be taken with food.

Dosage of Nifurtimox in Pediatric Patients (birth[a] to less than 18 years of age)

Body Weight Group	Total Daily Dose of Nifurtimox (mg/kg)
40 kg or greater	8 to 10
Less than 40 kg	10 to 20

[a]Term newborn with body weight greater than or equal to 2.5 kg.

- Administer nifurtimox tablets orally three times daily with food for 60 days.
- Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with nifurtimox.
- See the manufacturer's labeling for additional important administration instructions, including individualized dosages based on increments of body weight.

Cautions

Contraindications.

- Known hypersensitivity to nifurtimox or to any of the excipients in nifurtimox.
- Alcohol consumption during treatment.

Warnings/Precautions.

Potential for Genotoxicity and Carcinogenicity.

Genotoxicity. Genotoxicity of nifurtimox has been demonstrated in humans, in vitro in several bacterial species and mammalian cell systems, and in vivo in rodents.

A study evaluating the cytogenetic effect of nifurtimox in pediatric patients ranging from 7 months to 14 years of age with Chagas disease demonstrated a 13-fold increase in chromosomal aberrations.

Carcinogenicity. Carcinogenicity has been observed in mice and rats treated chronically with nitrofuran agents which are structurally similar to nifurtimox. Similar data have not been reported for nifurtimox. It is not known whether nifurtimox is associated with carcinogenicity in humans.

Embryofetal Toxicity. Based on findings from animal studies, nifurtimox can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, nifurtimox administered orally to pregnant mice, rats, and rabbits during organogenesis was associated with reduced fetal body weights in rodents, and abortions, fetal death, and smaller litter sizes in rabbits at doses approximately equivalent to and 2 times, respectively, the maximum recommended human dose (MRHD) of 10 mg/kg/day. Fetal malformations were observed in pregnant rabbits administered nifurtimox doses less than the MRHD.

Advise pregnant women of the potential risk to a fetus. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with nifurtimox. Advise females of reproductive potential to use effective contraception during treatment with nifurtimox and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use condoms during treatment and for 3 months after the last dose of nifurtimox.

Worsening of Neurologic and Psychiatric Conditions. Patients with a history of brain injury, seizures, psychiatric disease, or serious behavioral alterations may experience

worsening of their conditions when receiving nifurtimox. Administer nifurtimox under close medical supervision in these patients and in patients who develop neurologic disturbances or psychiatric drug reactions.

Hypersensitivity. Cases of hypersensitivity have been reported in patients receiving therapy with nifurtimox. The hypersensitivity could be a reaction induced by nifurtimox or an immune response triggered by Chagas disease during treatment. Hypersensitivity reactions could be accompanied by hypotension, angioedema (including laryngeal or facial edema), dyspnea, pruritus, rash, or other severe skin reactions. At the first sign of serious hypersensitivity, discontinue treatment with nifurtimox.

Decreased Appetite and Weight Loss. Decreased appetite and weight loss were reported in patients treated with nifurtimox in clinical trials. During treatment with nifurtimox, patients can lose their appetite or experience nausea/vomiting, which can result in weight loss. Check body weight every 14 days, as dosage adjustment may be necessary.

Porphyria. Treatment with nitrofuran derivatives such as nifurtimox may precipitate acute attacks of porphyria. Administer nifurtimox tablets under close medical supervision in patients with porphyria.

Specific Populations.

Pregnancy. *Risk Summary:* Based on animal studies, nifurtimox may cause fetal harm when administered to a pregnant woman. Published postmarketing reports on nifurtimox use during pregnancy are insufficient to inform a drug-associated risk of birth defects and miscarriage. There are risks to the fetus associated with Chagas disease.

Nifurtimox administered orally to pregnant mice, rats, and rabbits during organogenesis was associated with reduced fetal body weights in mice, reduced maternal and fetal body weights in rats, and abortions, reduced maternal weight gain, and reduced numbers of live fetuses in rabbits when nifurtimox was administered orally during organogenesis at doses approximately equal to the MRHD in rodents and 2 times the MRHD in rabbits. An increased incidence of a fetal skeletal malformation (fusion of caudal vertebral bodies) occurred in rabbits at nifurtimox doses approximately 0.2 times the MRHD. In a pre-postnatal study, maternal body weights and fetal body weights of first generation offspring were reduced at doses approximately equal to or 0.5 times the MRHD, respectively, and several male offspring in the nifurtimox treatment groups exhibited slightly small testes at doses ≥0.2 times the MRHD. Advise pregnant women of the potential risk to a fetus.

There is a pregnancy safety study for nifurtimox. If nifurtimox is administered during pregnancy, or if a patient becomes pregnant while receiving nifurtimox or within six months following the last dose of nifurtimox, healthcare providers should report nifurtimox exposure by calling 1-888-842-2937.

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.

Disease-associated Maternal and/or Embryofetal Risk: Published data from case-control and observational studies on chronic Chagas disease during pregnancy are inconsistent in their findings. Some studies showed an increased risk of pregnancy loss, prematurity, and neonatal mortality in pregnant women who have chronic Chagas disease, while other studies did not demonstrate these findings. Chronic Chagas disease is usually not immediately life-threatening. Since pregnancy findings are inconsistent, treatment of chronic Chagas disease during pregnancy is not recommended due to risk of embryofetal toxicity from nifurtimox.

Acute symptomatic Chagas disease is rare in pregnant women; however, symptoms may be serious or life-threatening. If a pregnant woman presents with acute symptomatic Chagas disease, the risks versus benefits of treatment with nifurtimox to the mother and the fetus should be evaluated on a case-by-case basis.

Animal Data: In preliminary embryo-fetal studies, pregnant mice and rats were administered 20, 50, and 125 mg/kg/day nifurtimox during the period of organogenesis (gestation day [GD] 6 to GD 15 for both species). Maternal body weights were significantly reduced in the 50 and 125 mg/kg/day dose groups in rats, but not in mice. No fetal malformations were reported for either species, but mean fetal weights were significantly reduced in the 125 mg/kg/day dose group in mice and in the 50 and 125 mg/kg/day dose groups in rats. No maternal toxicity was observed in mice at 125 mg/kg/day or in rats at 20 mg/kg/day (respectively approximately equal to or 0.3 times the MRHD based on body surface area comparison). No adverse fetal effects were observed in mice at a dose of 50 mg/kg/day or in rats at a dose of 20 mg/kg/day (respectively equivalent to 0.4 times or 0.3 times the MRHD based on body surface area comparison).

In pregnant rabbits administered 5, 15, and 60 mg/kg/day nifurtimox during the period of organogenesis (GD 6 to GD 20), the high dose was associated with maternal toxicity including reduced body weights and food consumption, and abortions in 8/20 high-dose dams. The mean number of live fetuses per litter and the percent of live fetuses per total implantations per group were significantly lower in the mid- and high-dose groups compared to the control group. Nifurtimox administration was associated with increased fetal and litter incidences of a skeletal malformation (fusion of caudal vertebral bodies) in fetuses in the low-dose group receiving 5 mg/kg/day (approximately equivalent to 0.2 times the MRHD based on body surface area comparison). No maternal toxicity was observed at 15 mg/kg/day, which

is approximately equivalent to 0.5 times the MRHD based on body surface area comparison.

In a pre-postnatal study, pregnant female rats were administered 15, 30, and 60 mg/kg/day nifurtimox during organogenesis and lactation (GD 6 to lactation day [LD] 21). Maternal findings included reduced maternal body weights in high-dose dams during gestation and to a lesser degree during lactation. In first-generation offspring, body weights were significantly reduced in males and females in the high-dose group during the lactation and post-lactation periods. Physical development, neurological function, and reproduction of first-generation offspring were not substantially changed in the nifurtimox treatment groups, but 5–20% of male offspring in all the nifurtimox treatment groups exhibited slightly small testes. No adverse maternal effects or fetal effects on first-generation female offspring occurred at 30 mg/kg/day, and no adverse fetal effects on the development of male offspring occurred at 15 mg/kg/day (respectively approximately 0.5 and 0.2 times the MRHD based on body surface area comparison).

Lactation. Published literature demonstrates that nifurtimox is present in human breast milk with an estimated infant daily dose of less than 15% of the recommended daily dose for pediatric patients with Chagas disease. There were no reports of adverse effects on the small number of infants who were breastfed by mothers taking nifurtimox. There is no information on the effects of nifurtimox on milk production. Monitor infants exposed to nifurtimox through breast milk for vomiting, rash, decreased appetite, pyrexia, and irritability.

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

Females and Males of Reproductive Potential. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with nifurtimox.

Nifurtimox may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with nifurtimox and for 6 months after the final dose.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use condoms during treatment and for 3 months after the final dose of nifurtimox.

Based on findings in rodents, nifurtimox may impair fertility in males of reproductive potential. These effects on fertility were not reversible in 75% of the animals at 11 weeks after dosing.

Pediatric Use. The safety and effectiveness of nifurtimox have been established for the treatment of Chagas disease (American trypanosomiasis) caused by *Trypanosoma cruzi* in pediatric patients from birth to less than 18 years of age weighing at least 2.5 kg.

The safety and effectiveness of nifurtimox have not been established in pediatric patients weighing less than 2.5 kg.

Renal Impairment. The effect of renal impairment on the pharmacokinetics of nifurtimox is unknown. Published literature suggests that blood concentrations of nifurtimox were increased in patients with end-stage renal disease (ESRD) requiring hemodialysis. Administer nifurtimox under close medical supervision.

Hepatic Impairment. The effect of hepatic impairment on the pharmacokinetics of nifurtimox is unknown.

Administer nifurtimox under close medical supervision.

Common Adverse Effects. The most frequently reported adverse reactions (≥5%) are vomiting, abdominal pain, headache, decreased appetite, nausea, pyrexia, and rash.

Interactions

Specific Drugs. It is *essential* that the manufacturer's labeling be consulted for more detailed information on interactions with this drug, including possible dosage adjustments. Interaction highlights:

Concomitant use of nifurtimox with alcohol may increase the incidence and severity of undesirable effects similar to other nitrofurans and nitroheterocyclic compounds. Nifurtimox is contraindicated in patients who consume alcohol during treatment.

Actions

Mechanism of Action.

- Nifurtimox is an antiprotozoal drug.
- The mechanism of action of nifurtimox is not fully understood. Studies suggest that nifurtimox is metabolized/activated by type I (oxygen insensitive) and type II (oxygen sensitive) nitoreductases (NTR), leading to production of toxic intermediate metabolites and/or reactive oxygen species that induce DNA damage and cell death of both intracellular and extracellular forms of *T. cruzi*.

Spectrum.

- Nifurtimox is active against all three stages (trypomastigotes, amastigotes, and epimastigotes) of *T. cruzi*. However, the sensitivity of *T. cruzi* strains to nifurtimox from different geographic regions may vary.

Resistance.

- In vitro studies suggest the potential for development of resistance in *T. cruzi* against nifurtimox.
- The mechanism of resistance to nifurtimox appears to be multifactorial. Trypanosomal nitroreductase is defined as a key resistance determinate. Either loss of gene copy, mutation of gene or down-regulation of gene expression are sufficient to cause decreased susceptibility of *T. cruzi* against nitroheterocyclic drugs like nifurtimox. In addition, other mechanisms of resistance like lower drug influx or higher

drug efflux are described. However, the clinical relevance of these findings is not known.
- Nonclinical studies suggest cross-resistance between nifurtimox and benznidazole. This appears to be due to down regulation of type I NTR localized in the mitochondria.

Advice to Patients

Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Embryofetal Toxicity.
- Advise pregnant women and females of reproductive potential of the potential risk of nifurtimox to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception while taking nifurtimox and for 6 months after the last dose.
- Advise male patients with female partners of reproductive potential to use condoms during treatment with nifurtimox and for 3 months after the final dose of nifurtimox.

Lactation.
- Advise nursing mothers to monitor infants exposed to nifurtimox through breast milk for vomiting, rash, decreased appetite, fever, and irritability.

Infertility.
- Advise males of reproductive potential that nifurtimox may impair fertility.

Worsening of Neurologic and Psychiatric Conditions.
- Advise patients with a history of brain injury, seizures, psychiatric disease, serious behavioral alterations or if neurologic and/or psychiatric drug reactions occur, that nifurtimox tablets should be administered only under close medical supervision.

Hypersensitivity.
- Inform patients that hypersensitivity could be a reaction caused by nifurtimox or an immune response triggered by Chagas disease during treatment. Hypersensitivity reactions could include hypotension, angioedema (including laryngeal or facial edema), dyspnea, pruritus, rash, or other severe skin reactions.

Alcohol Consumption.
- Advise patients to discontinue alcohol use during treatment with nifurtimox. Nifurtimox is contraindicated in patients who consume alcohol during treatment.

Decreased Appetite and Weight Loss.
- Inform patients that nifurtimox can cause decreased appetite and weight loss. Body weight should be checked every 14 days, as the dosage may have to be adjusted.

Porphyria.
- Advise patients with porphyria that treatment with nitrofuran derivatives, such as nifurtimox, may precipitate acute attacks of porphyria. Administer nifurtimox tablets under close medical supervision in patients with porphyria.

Important Administration Instructions.
- Advise patients to take nifurtimox with food.
- Advise patients not to break nifurtimox tablets mechanically with a tablet splitting device.
- For patients who cannot swallow tablets, nifurtimox can be dispersed in water and administered as a slurry, taken with food.

Ability to Operate Vehicles or Machinery.
- Inform patients that if muscle weakness or tremors occur during treatment with nifurtimox they should not drive, cycle, or use any tools or machines.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Nifurtimox	
Oral	
Tablets, Film-coated	
30 mg	
	Lampit® (scored), Bayer
120 mg	
	Lampit® (scored), Bayer