

NITROFURANTOIN - nitrofurantoin suspension

ANI Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NITROFURANTOIN ORAL SUSPENSION safely and effectively. See full prescribing information for NITROFURANTOIN ORAL SUSPENSION.

NITROFURANTOIN oral suspension

Initial U.S. Approval: 1953

RECENT MAJOR CHANGES

Dosage and Administration (2)

1/2024

INDICATIONS AND USAGE

Nitrofurantoin is a nitrofuran antibacterial indicated in adults and pediatric patients 1 month of age and older for the treatment of urinary tract infections caused by susceptible bacteria. (1) (1)

Limitations of Use (1)

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses. (1) (1)

Usage (1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nitrofurantoin and other antibacterial drugs, nitrofurantoin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1) (1)

DOSAGE AND ADMINISTRATION

- Adult Patients: 50 mg to 100 mg four times a day -the lower dosage level is recommended for uncomplicated urinary tract infections. (2.2)
- Pediatric Patients: 5 mg/kg to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age). (2.3)

DOSAGE FORMS AND STRENGTHS

Oral Suspension: 25 mg/5 mL. (3) (3)

CONTRAINDICATIONS

- Known hypersensitivity to nitrofurantoin. (4)
- History of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin. (4)
- Patients who have anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine). (4)
- Pregnant patients at term (38 weeks to 42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. (4)
- Pediatric Patients under one month of age. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving nitrofurantoin. If signs and symptoms of a hypersensitivity reaction occurs, immediately discontinue nitrofurantoin. (5.1)
- Pulmonary Reactions: Discontinue if sign and symptoms of pulmonary reactions occur and take appropriate measures. (5.2)
- Hepatotoxicity: Discontinue if signs/symptoms of hepatitis occur. Monitor liver function tests. (5.3)
- Neuropathy: Peripheral neuropathy has occurred. (5.4)
- Hemolytic Anemia: Discontinue if sign and symptoms of hemolysis occur. (5.5)
- *Clostridioides difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.6)

ADVERSE REACTIONS

The most common adverse reactions occurring in patients are nausea, vomiting, anorexia, vertigo, nystagmus, dizziness, headache, angioedema, rash, urticaria, pulmonary hypersensitivity reactions, hepatic reactions, peripheral neuropathy, increased aspartate aminotransferase, increased alanine aminotransferase, decreased hemoglobin, increased serum phosphorus, and eosinophilia (6) (6)

To report SUSPECTED ADVERSE REACTIONS, contact ANI Pharmaceuticals, Inc. at 1-855-204-1431 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- Antacids: Decreased absorption of nitrofurantoin. (7.1)
- Uricosuric drugs: Inhibit renal tubular secretion of nitrofurantoin. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding is not recommended in infants under one month of age or with glucose-6-phosphate dehydrogenase (G6PD) deficiency. (8.2)
- Pediatric Use: Nitrofurantoin is contraindicated in pediatric patients under one month of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

Nitrofurantoin is indicated in adults and pediatric patients 1 month of age and older for the treatment of urinary tract infections due to susceptible strains of *Escherichia coli*, *Enterococcus* species, *Staphylococcus aureus*, *Klebsiella* species and *Enterobacter* species.

Limitations of Use

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses [see *Warnings and Precautions (5.7)*].

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nitrofurantoin and other antibacterial drugs, nitrofurantoin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE & ADMINISTRATION

2.1 Recommended Dosage and Administration in Adult Patients

The recommended dosage is 50 mg to 100 mg of nitrofurantoin four times a day.

For long-term suppressive therapy in adults, a reduction of dosage to 50 mg to 100 mg at bedtime may be adequate. The benefits of long-term suppressive therapy should be balanced against the increased potential for systemic toxicity and for the development of antibacterial resistance [see *Warnings and Precautions (5.2, 5.4, 5.6)*].

Administer nitrofurantoin with food to improve drug absorption [see *Clinical Pharmacology (12.3)*] and, in some patients, tolerance.

2.2 Recommended Dosage and Administration in Pediatric Patients (1 month of age and older)

The recommended dosage of nitrofurantoin is 5 mg/kg to 7 mg/kg of body weight per

24 hours, given in four divided doses in pediatric patients aged 1 month and older. Administer nitrofurantoin with food to improve drug absorption [see *Clinical Pharmacology (12.3)*] and, in some patients, tolerance.

Table 1 lists individual dosage volumes for nitrofurantoin oral suspension (25 mg/5 mL) based on body weight for pediatric patients.

Table 1: Nitrofurantoin Oral Suspension Pediatric Dosing Table for Pediatric Patients 1 month of Age and Older

| Weight in Kilograms (kg) | Pediatric Doses (mL), Frequency: Four times Daily |
|-----------------------------|---|
| | 25 mg/5 mL oral suspension |
| 4 kg or lower | 1 |
| Greater than 4 kg to 5 kg | 1.4 |
| Greater than 5 kg to 7 kg | 1.8 |
| Greater than 7 kg to 10 kg | 2.5 |
| Greater than 10 kg to 14 kg | 3.5 |
| Greater than 14 kg to 20 kg | 5 |
| Greater than 20 kg to 25 kg | 7 |
| Greater than 25 kg to 30 kg | 8.5 |
| Greater than 30 kg to 40 kg | 10 |
| 40 kg or greater | See Adult Dose |

To measure the correct pediatric doses, it is important to administer nitrofurantoin oral suspension with an appropriate size oral dosing syringe with graduations that align with the volume prescribed in Table 1 above.

Continue therapy for one week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for reevaluation.

For long-term suppressive therapy in pediatric patients, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate [see *Warnings and Precautions (5.2, 5.4, 5.6)*].

3 DOSAGE FORMS & STRENGTHS

Nitrofurantoin Oral Suspension, USP is available as a lemon-yellow liquid with cherry

flavor, free from extraneous particles for oral suspension containing 25 mg/5 mL of nitrofurantoin.

4 CONTRAINDICATIONS

Nitrofurantoin is contraindicated in:

- patients with known hypersensitivity to nitrofurantoin [*see Warnings and Precautions (5.1)*].
- patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin [*see Warnings and Precautions (5.3)*].
- patients who have anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) due to an increased risk of toxicity resulting from impaired excretion of the drug [*see Warnings and Precautions (5.4)*].
- pregnant patients at term (38 weeks to 42 weeks gestation), during labor and delivery, or when the onset of labor is imminent and in pediatric patients younger than 1 month of age because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability) [*see Warnings and Precautions (5.5) and Use in Specific Populations (8.1 and 8.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving nitrofurantoin [*see Adverse Reactions (6)*]. If signs and symptoms of a hypersensitivity reaction occurs, immediately discontinue nitrofurantoin and initiate appropriate medications and/or supportive care. Nitrofurantoin is contraindicated in patients with known hypersensitivity to nitrofurantoin.

5.2 Pulmonary Reactions

Acute, subacute, or chronic pulmonary reactions have been reported in patients treated with nitrofurantoin. If these reactions occur, discontinue nitrofurantoin and take appropriate measures. Reports have cited pulmonary reactions as a contributing cause of death.

Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) can develop insidiously. These reactions occur generally in patients receiving therapy for six months or longer. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighed against potential risks [*see Adverse Reactions (6)*].

5.3 Hepatotoxicity

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, has occurred. Fatalities have been reported. The onset of chronic active hepatitis may be insidious. Monitor patients periodically for changes in biochemical

tests that would indicate liver injury. If hepatitis occurs, discontinue nitrofurantoin immediately, and take appropriate measures.

5.4 Neuropathy

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Monitor patients receiving long-term therapy periodically for changes in renal function.

Optic neuritis has been reported with nitrofurantoin formulations [see *Adverse Reactions (6)*].

5.5 Hemolytic Anemia

Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. If hemolysis occurs, discontinue nitrofurantoin immediately; hemolysis ceases when the drug is withdrawn.

5.6 Clostridioides difficile-associated Diarrhea

Clostridioides difficile-associated Diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including nitrofurantoin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

5.7 Persistence or Reappearance of Bacteriuria

Nitrofurantoin lacks the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with nitrofurantoin are predisposed to persistence or reappearance of bacteriuria. If persistence or reappearance of bacteriuria occurs with symptoms of urinary tract infection, after treatment with nitrofurantoin, other therapeutic agents with broader

tissue distribution should be selected. In considering the use of nitrofurantoin, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antibacterial resistance when agents with broader tissue distribution are utilized.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions (5.1)*]
- Pulmonary Reactions [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Neuropathy [*see Warnings and Precautions (5.4)*]
- Hemolytic anemia [*see Warnings and Precautions (5.5)*]
- *Clostridioides difficile*-associated Diarrhea [*see Warnings and Precautions (5.6)*]
- Persistence or Reappearance of Bacteriuria [*see Warnings and Precautions (5.7)*]

The following adverse reactions associated with the use of nitrofurantoin formulations, including nitrofurantoin oral suspension, were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory: chronic, subacute, or acute pulmonary hypersensitivity reactions have occurred.

Chronic pulmonary reactions have occurred generally in patients who have received continuous treatment for six months or longer. Malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations which can occur insidiously. Radiologic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations of the chronic pulmonary reaction. Fever is prominent.

The severity of chronic pulmonary reactions and their degrees of resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be impaired permanently, even after cessation of therapy. The risk is greater when chronic pulmonary reactions are not recognized early.

In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months. If the symptoms are not recognized as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation of pleural effusion on x-ray, and eosinophilia. Acute reactions usually occur within the first week of treatment and are

reversible with cessation of therapy. Resolution often is dramatic.

Changes in EKG (e.g., non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions.

Cyanosis has been reported.

Hepatic: Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, have occurred.

Neurologic: Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility of peripheral neuropathy.

Asthenia, vertigo, nystagmus, dizziness, headache, and drowsiness also have been reported with the use of nitrofurantoin.

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported. Bulging fontanels, as a sign of benign intracranial hypertension in infants, have been reported rarely.

Dermatologic: Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported. Alopecia also has been reported.

Allergic: A lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; pruritus; urticaria; anaphylaxis; arthralgia; myalgia; drug fever; and vasculitis (sometimes associated with pulmonary reactions) have been reported. Hypersensitivity reactions present the most frequent spontaneously-reported adverse reactions in worldwide post marketing experience with nitrofurantoin formulations, including nitrofurantoin oral suspension.

Gastrointestinal: Nausea, emesis, and anorexia occur most often. Abdominal pain and diarrhea are less common gastrointestinal reactions. These dose-related reactions can be minimized by reduction of dosage. Sialadenitis and pancreatitis have been reported. There have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.

Hematologic: Cyanosis secondary to methemoglobinemia has been reported.

Miscellaneous: As with other antibacterial agents, superinfections caused by resistant

organisms, e.g., *Pseudomonas* species or *Candida* species, can occur. There are sporadic reports of *Clostridioides difficile* superinfections, or pseudomembranous colitis, with the use of nitrofurantoin, including nitrofurantoin oral suspension.

Laboratory Adverse Reactions

The following laboratory adverse reactions have been reported with the use of nitrofurantoin formulations, including nitrofurantoin oral suspension; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia, agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported.

7 DRUG INTERACTIONS

7.1 Antacids

Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of nitrofurantoin onto the surface of magnesium trisilicate. If coadministration of nitrofurantoin with antacids containing magnesium trisilicate cannot be avoided, monitor for lack of efficacy [see *Clinical Pharmacology* (12.3)].

7.2 Uricosuric Drugs

Uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. The resulting increase in nitrofurantoin serum levels may increase toxicity, and the decreased urinary levels could lessen its efficacy as a urinary tract antibacterial. Therefore, monitor for nitrofurantoin adverse reactions when co-administering nitrofurantoin with uricosuric drugs.

7.3 Drug Interference with Laboratory Tests

The presence of nitrofurantoin can cause a false-positive reaction for glucose in the urine when using Benedict's or Fehling's copper reduction reaction to determine the amount of reducing substances like glucose in the urine. Use glucose tests based on enzymatic glucose oxidase reactions to detect glucose in the urine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Nitrofurantoin is contraindicated in pregnant women at term (38 weeks to 42 weeks gestation), during labor and delivery, or when the onset of labor is imminent because of the possibility of hemolytic anemia in the infant (see *Clinical Considerations*).

Published epidemiological studies, including cohort studies and case control studies, have reported inconsistent findings related to nitrofurantoin use during the first trimester and risk of major birth defects. These studies cannot definitively establish the presence or absence of risk due to several methodological limitations. The limited number of epidemiological studies available have not identified drug-associated risks of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies, no fetotoxicity was observed when nitrofurantoin was administered orally to pregnant rats and rabbits, during organogenesis, at up to 6 times the recommended human dose (see *Data*).

The 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

Fetal/Neonatal Adverse Reactions

Nitrofurantoin is not recommended in pregnant women at term (38 weeks to 42 weeks gestation), during labor and delivery, or when the onset of labor is imminent because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability) [see *Contraindications (4)* and *Warnings and Precautions (5.4)*].

Data

Animal Data

Several reproduction studies have been performed in rabbits and rats at doses up to six times the human dose and have revealed no harm to the fetus due to nitrofurantoin. In a single published study conducted in mice at 68 times the human dose (based on mg/kg administered to the dam), growth retardation and a low incidence of minor and common malformations were observed. However, at 25 times the human dose, fetal malformations were not observed.

Nitrofurantoin has been shown in one published transplacental carcinogenicity study to induce lung papillary adenomas in the F1 generation mice at doses 19 times the human dose on a mg/kg basis. The relationship of this finding to potential human carcinogenesis is presently unknown.

8.2 Lactation

Risk Summary

Nitrofurantoin is present in human breast milk following oral administration. There are insufficient data on the effect of nitrofurantoin on milk production.

Infants less than one month of age or who have glucose-6-phosphate dehydrogenase

(G6PD) deficiency are at risk for hemolytic anemia from nitrofurantoin exposure. Therefore, breastfeeding is not recommended in these infants.

In a breastfed infant over the age of one month and with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for nitrofurantoin and any potential adverse effects on the breastfed infant from nitrofurantoin or from the underlying maternal condition. Monitor these infants for vomiting, diarrhea, and rash.

8.3 Females and Males of Reproductive Potential

Infertility

Male

Based on findings from a fertility study conducted in 36 healthy male volunteers and an animal fertility study, nitrofurantoin may reversibly decrease spermatogenesis [see *Nonclinical Toxicology (13.1)*]. Nitrofurantoin doses of 10 mg/kg/day or greater in healthy human males may produce a slight to moderate spermatogenic arrest with a decrease in sperm count. The effect on fertility is unknown.

8.4 Pediatric Use

Nitrofurantoin is contraindicated in pediatric patients younger than 1 month of age because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability). [see *Contraindications (4) and Warnings and Precautions (5.4)*].

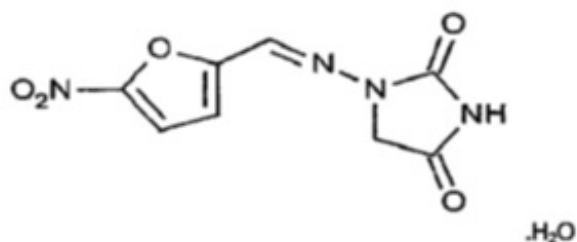
The safety and effectiveness of nitrofurantoin in pediatric patients aged 1 month of age and older for the treatment of urinary tract infections have been established.

10 OVERDOSAGE

Incidents of acute overdosage of nitrofurantoin have resulted in symptoms such as vomiting. Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug. Nitrofurantoin is dialyzable.

11 DESCRIPTION

Nitrofurantoin Oral Suspension, USP contains nitrofurantoin, a synthetic nitrofuran antibacterial agent specific for urinary tract infections. The chemical name is 1-[[[(5-nitro-2-furanyl)methylene]amino]-2,4imidazolidinedione monohydrate. The molecular formula is C₈H₆N₄O₅·H₂O and the molecular weight is 256.17. The structural formula is:



Nitrofurantoin is a stable, yellow, crystalline compound.

Nitrofurantoin Oral Suspension, USP is available as a lemon-yellow liquid with cherry flavor, free from extraneous particles for oral administration containing 25 mg/5 mL of nitrofurantoin. Nitrofurantoin Oral Suspension, USP also contains the following inactive ingredients: citric acid, artificial cherry flavor, glycerin, methylparaben, propylparaben, purified water, sodium citrate, sucralose, simethicone emulsion, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitrofurantoin is an antibacterial drug [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Pharmacodynamic effects of nitrofurantoin are unknown.

12.3 Pharmacokinetics

Absorption

Orally administered nitrofurantoin is readily absorbed. Blood concentrations at therapeutic dosage are usually low.

Effect of Food

The presence of food or agents delaying gastric emptying can increase the bioavailability of nitrofurantoin.

Distribution

Nitrofurantoin is highly soluble in urine. Nitrofurantoin lacks the broader tissue distribution of other therapeutic agents approved for urinary tract infections.

Elimination

Excretion

Nitrofurantoin is rapidly excreted in urine, to which it may impart a brown color.

Following a dose regimen of 100 mg four times a day for 7 days, average urinary drug recoveries (0 hour to 24 hours) on Day 1 and Day 7 were 42.7% and 43.6%

Nitrofurantoin is dialyzable.

Specific Populations

The pharmacokinetics of nitrofurantoin are unknown for the geriatric patients, pediatric patients, patients with hepatic impairment, or pregnant women. Differences between male and female patients, and racial or ethnic groups are unknown.

Patients with Renal Impairment

The reported urinary recoveries of nitrofurantoin after a single 100 mg oral dose and 100 mg four times a day in patients with varying renal function showed approximate linear relationship between the amount of nitrofurantoin recovered and creatinine clearance.

Drug Interaction Studies

Antacids such as magnesium trisilicate

In a cross-over study, the *in vivo* absorption characteristics of nitrofurantoin and nitrofurantoin-magnesium trisilicate combination were evaluated in 6 healthy males. The administration of 5 g magnesium trisilicate with 100 mg nitrofurantoin reduced the rate and extent of nitrofurantoin excretion reflecting decrease in both rate and extent of its absorption [see *Drug Interaction (7.1)*].

Propantheline

In a crossover study, the *in vivo* absorption characteristics of nitrofurantoin and propantheline (an anticholinergic agent) combination were evaluated in six subjects. Administration of 30 mg of propantheline 45 min prior to nitrofurantoin 100 mg administration resulted in a statistically significant increase in nitrofurantoin excretion, however, the clinical significance of this effect is unknown.

12.4 Microbiology

Mechanism of Action

Nitrofurantoin is reduced by a wide range of enzymes including bacterial flavoproteins to reactive intermediates which are damaging to macromolecules such as DNA and proteins.

Resistance

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species. Although cross-resistance with other antibacterials may occur, cross resistance with sulfonamides has not been observed.

Interaction with Other Antibacterials

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolones.

Antibacterial Activity

Nitrofurantoin has been shown to be active against most of the following bacteria both *in vitro* and in clinical infections:

Aerobic bacteria

Gram-positive bacteria

Staphylococcus aureus

Enterococcus species

Gram-negative bacteria

Escherichia coli

Enterobacter species

Klebsiella species

The following *in vitro* data are available, but their clinical significance is unknown.

Nitrofurantoin exhibits *in vitro* activity against the following bacteria; however, the safety and efficacy of nitrofurantoin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic bacteria

Gram-positive bacteria

Coagulase-negative staphylococci (including *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*)

Streptococcus agalactiae

Viridans group streptococci

Gram-negative bacteria

Citrobacter koseri

Citrobacter freundii

Klebsiella oxytoca

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see: <http://www.fda.gov/STIC>.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility

Carcinogenesis

Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks. Two chronic rodent bioassays utilizing male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female B6C3F1 mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there were increased incidences of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the subcutaneous tissue.

The significance of carcinogenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

Mutagenesis

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations in L5178Y mouse lymphoma cells. Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells but not in human cells in culture. Results of the sex-linked recessive lethal assay in *Drosophila* were negative after administration of nitrofurantoin by feeding or by injection. Nitrofurantoin did not induce heritable mutation in the rodent models examined.

The significance of mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

Impairment of Fertility

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Nitrofurantoin Oral Suspension, USP 25 mg/5 mL is available in:

230 mL PET amber bottle

NDC 70954-496-10

Storage and Handling

Avoid exposure to strong light which may darken the drug. It is stable when stored between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect from freezing. Shake vigorously.

Dispense in tight, light-resistant, plastic (PET) or glass container.

Use within 30 days.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Administration Instructions

Instruct the patients to:

- complete the full course of therapy; however, advise the patients or their caregiver to contact their physician if any unusual symptoms occur during therapy.
- take daily doses of nitrofurantoin with food, as food will further enhance tolerance and improve the absorption of the drug.
- shake nitrofurantoin oral suspension vigorously before use each time.
- use an oral dosing syringe to correctly measure the prescribed amount of nitrofurantoin oral suspension. Inform patients or caregivers that an appropriate size oral dosing syringe with graduations that align with the volume prescribed may be obtained from their pharmacy.

Serious Allergic Reactions

Advise patients that allergic reactions, including serious allergic reactions, could occur with nitrofurantoin and that serious reactions require immediate treatment. Advise patients to discontinue nitrofurantoin at the first sign of allergic reactions [see *Warnings and Precautions (5.1)*].

Diarrhea

Advise patients that diarrhea is a common problem caused by antibacterial drugs, including nitrofurantoin which usually ends when the antibacterial drug is discontinued. Sometimes frequent watery and bloody diarrhea (with or without stomach cramps and fever) may occur even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, advise patients to contact their physician as soon as possible [see *Warnings and Precautions (5.6)*].

Drug Interactions with Antacids

Advise patients not to use antacid preparations containing magnesium trisilicate while taking nitrofurantoin [see *Drug Interactions (7.1)*].

Lactation

Advise women not to breastfeed infants who are less than one month of age or who have G6PD deficiency during treatment with nitrofurantoin [see *Use in Specific Populations (8.2)*].

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including nitrofurantoin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When nitrofurantoin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by nitrofurantoin or other antibacterial drugs in the future.

Change in Urine Color

Inform patients that nitrofurantoin may impart a brown color to their urine [*see Clinical Pharmacology (12.3)*].

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Issued: 03/2024

LB4487-01

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Nitrofurantoin Oral Suspension, USP 25 mg/5 mL

NDC 70954-496-10 -- 230 mL

Container Label

NDC 70954-496-10

Nitrofurantoin Oral Suspension, USP

25 mg/5 mL

Urinary Tract Antibacterial



Rx only
230 mL

Each 5 mL contains 25 mg of nitrofurantoin.
SHAKE VIGOROUSLY.

Recommended Dosage: See Prescribing Information.

For Patients: Date of first opening

____/____/____

Discard unused portion 30 days after first opening.
Dispense in tight, light-resistant, plastic (PET) or glass container.

Store between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Avoid exposure to strong light which may darken the drug.
Protect from freezing.

Keep out of reach of children.

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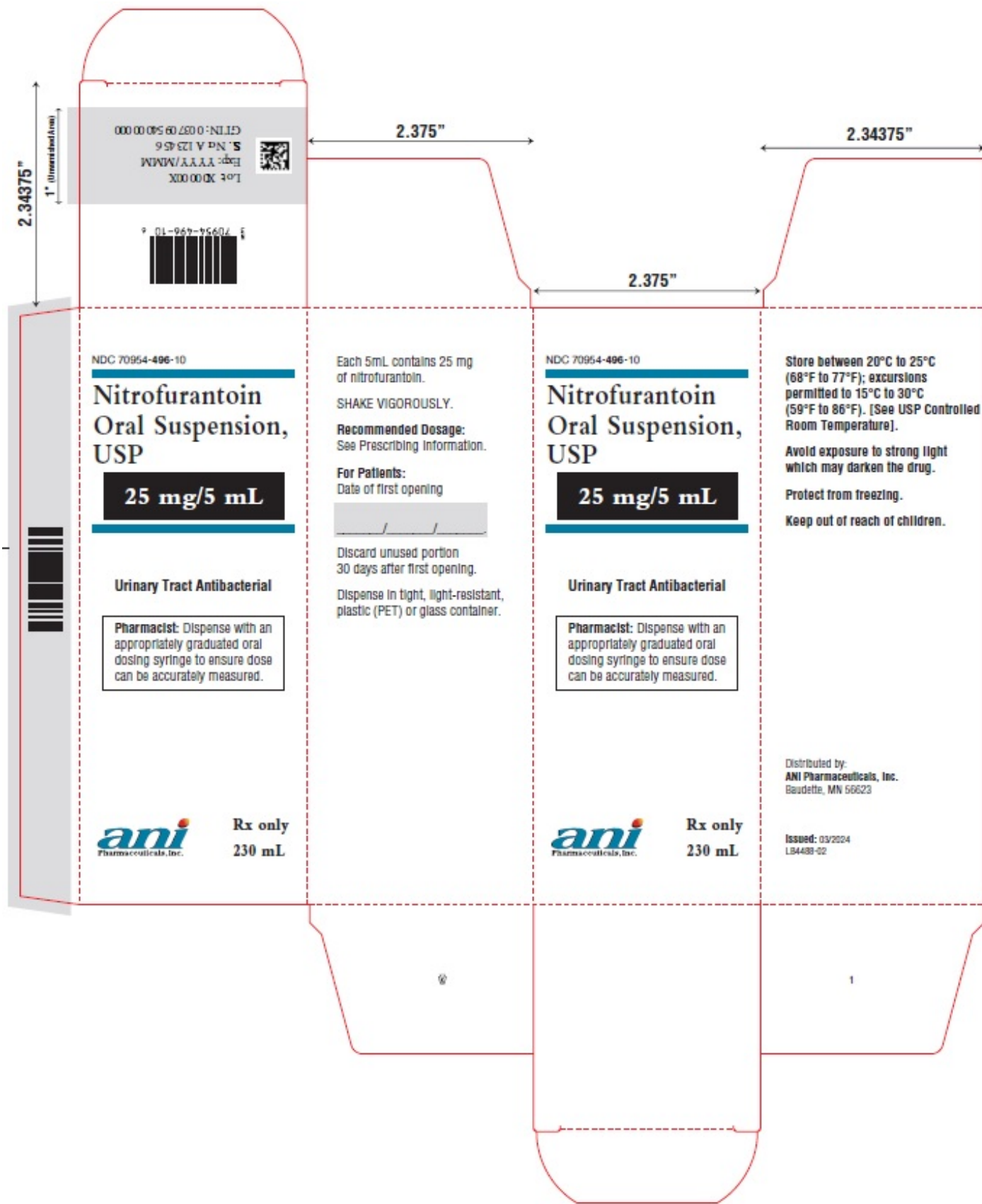
LB4486-01



Lot: X00000X
Exp: YYYY/MMMM
S. No.: A123456
GTIN: 00370954000000



Carton Label



NITROFURANTOIN
nitrofurantoin suspension

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:70954-496 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|--------------------------|-----------------|
| NITROFURANTOIN (UNII: 927AH8112L) (NITROFURANTOIN - UNII:927AH8112L) | NITROFURANTOIN | 25 mg in 5 mL |

Inactive Ingredients

| Ingredient Name | Strength |
|---|-----------------|
| CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP) | |
| GLYCERIN (UNII: PDC6A3C0OX) | |
| METHYLPARABEN (UNII: A2I8C7HI9T) | |
| PROPYLPARABEN (UNII: Z8IX2SC1OH) | |
| WATER (UNII: 059QF0KO0R) | |
| SODIUM CITRATE (UNII: 1Q73Q2JULR) | |
| SUCRALOSE (UNII: 96K6UQ3ZD4) | |
| XANTHAN GUM (UNII: TTV12P4NEE) | |
| DIMETHICONE (UNII: 92RU3N3Y1O) | |

Product Characteristics

| | | | |
|-----------------|-----------------------|---------------------|--|
| Color | YELLOW (Lemon Yellow) | Score | |
| Shape | | Size | |
| Flavor | CHERRY | Imprint Code | |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|----------|------------------|---|-----------------------------|---------------------------|
| 1 | NDC:70954-496-10 | 230 mL in 1 BOTTLE; Type 0: Not a Combination Product | 04/17/2023 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---------------------------|---|-----------------------------|---------------------------|
| ANDA | ANDA216385 | 04/17/2023 | |

Labeler - ANI Pharmaceuticals, Inc. (145588013)

Establishment

| Name | Address | ID/FEI | Business Operations |
|-------------|----------------|---------------|----------------------------|
|-------------|----------------|---------------|----------------------------|

| | | |
|------------------------|-----------|--|
| Novitium Pharma LLC | 080301870 | ANALYSIS(70954-496) , LABEL(70954-496) , MANUFACTURE(70954-496) , PACK(70954-496) |
|------------------------|-----------|--|

Revised: 3/2024

ANI Pharmaceuticals, Inc.