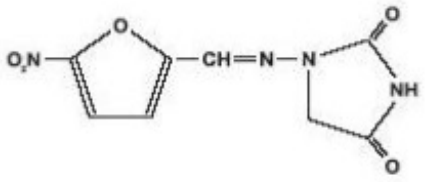
NITROFURANTOIN- nitrofurantoin suspension
Rising Pharma Holdings, Inc.

Nitrofurantoin Oral Suspension, USP

DESCRIPTION

Nitrofurantoin, a synthetic chemical, is a stable, lemon-yellow, crystalline powder. Nitrofurantoin oral suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin oral suspension, USPis available in 25 mg/5 mL liquid suspension for oral administration.



1-[[(5-nitro-2-furanyl)methylene]amino]-2, 4-imidazolidinedione

Inactive Ingredients

Nitrofurantoin oral suspension, USP contains banana flavor, carboxymethylcellulose sodium, citric acid monohydrate, glycerin, magnesium aluminum silicate, methylparaben, N&A mint flavor, non-crystallizing sorbitol solution, propylparaben, purified water and sodium citrate.

CLINICAL PHARMACOLOGY

Orally administered nitrofurantoin oral suspension is readily absorbed and rapidly excreted in urine. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine, to which it may impart a brown color.

Following a dose regimen of 100 mg q.i.d. for 7 days, average urinary drug recoveries (0 to 24 hours) on day 1 and day 7 were 42.7% and 43.6%.

Unlike many drugs, the presence of food or agents delaying gastric emptying can increase the bioavailability of nitrofurantoin oral suspension, presumably by allowing better dissolution in gastric juices.

Microbiology

Mode 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.

Cross-Resistance

Although cross-resistance with other antimicrobials may occur, cross resistance with sulfonamides has not been observed.

Interaction with Other Antimicrobials

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobial agents. Nitrofurantoin, in the form of nitrofurantoin oral suspension, has been shown to be active against most of the following bacteria both *in vitro* and in clinical infections: (See **INDICATIONS AND USAGE**).

Gram-positive Aerobes

Staphylococcus aureus

Enterococcus species

Gram-Negative Aerobes

Escherichia coli

NOTE: Some strains of *Enterobacter* species and *Klebsiella* species are resistant to nitrofurantoin.

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 effectiveness of nitrofurantoin in treating clinical infections due to these bacteria have not been established in adequate and well controlled clinical trials.

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

Streptococcus agalactiae

Viridans group streptococci

Gram-Negative Aerobes

Citrobacter koseri

Citrobacter freundii

Klebsiella oxytoca

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

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: https://www.fda.gov/STIC.

INDICATIONS AND USAGE

Nitrofurantoin oral suspension is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, *enterococci*, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

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

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with nitrofurantoin oral suspension are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with nitrofurantoin oral suspension, other therapeutic agents with broader tissue distribution should be selected. In considering the use of nitrofurantoin oral suspension, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

CONTRAINDICATIONS

Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.

Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38 to 42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.

Nitrofurantoin oral suspension is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin. Nitrofurantoin oral suspension is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

WARNINGS

Pulmonary reactions

ACUTE, SUBACUTE, OR CHRONIC PULMONARY REACTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH NITROFURANTOIN. IF THESE REACTIONS OCCUR, NITROFURANTOIN ORAL SUSPENSION SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. 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 RARELY AND 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 RESPIRATORY REACTIONS.)

Hepatotoxicity

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken.

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. Patients receiving long-term therapy should be monitored periodically for changes in renal function.

Optic neuritis has been reported rarely in postmarketing experience with nitrofurantoin formulations.

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. Hemolysis is an indication for discontinuing nitrofurantoin oral

suspension;hemolysis ceases when the drug is withdrawn.

Clostridium difficile-associated diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including nitrofurantoin oral suspension, 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 antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

Information for Patients

Patients should be advised to take nitrofurantoin oral suspension with food to further enhance tolerance and improve drug absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms should occur during therapy.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking nitrofurantoin oral suspension.

Drug Interactions

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.

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.

Drug/laboratory Test Interactions

As a result of the presence of nitrofurantoin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions but not with the glucose enzymatic test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 BDF^1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female $B6C3F_1$ 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. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 generation.

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations on 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 carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug. Doses of 10 mg/kg/day or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatogenic arrest with a decrease in sperm count.

Pregnancy

Teratogenic effects

Several reproduction studies have been performed in rabbits and rats at doses up to six times the human dose and have revealed no evidence of impaired fertility or 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; the relevance of these findings to humans is uncertain. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic effects

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. Because of the uncertainty regarding the human implications of these animal data, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

See **Contraindications**.

Nursing Mothers

Nitrofurantoin has been detected in human breast milk in trace amounts. Because of the potential for serious adverse reactions from nitrofurantoin in nursing infants under one month of age, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (see **CONTRAINDICATIONS**)

Pediatric Use

Safety and effectiveness of nitrofurantoin oral suspension in neonates below the age of one month have not been established. (see **CONTRAINDICATIONS**)

ADVERSE REACTIONS

Respiratory

CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR.

CHRONIC PULMONARY REACTIONS MAY OCCUR 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 RARELY 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. (see **WARNINGS**)

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 rarely.

Hepatic

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic neurosis, occur rarely. (see **WARNINGS**)

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 (see **WARNINGS**)

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

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported rarely. 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 rarely. Transient 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 events in world-wide postmarketing experience with nitrofurantoin formulations.

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 antimicrobial treatment. (see **WARNINGS**)

Hematologic

Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous

As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., *Pseudomonas* species or *Candida* species, can occur. There are sporadic reports of *Clostridium difficile* superinfections, or pseudomembranous colitis, with the use of nitrofurantoin.

Laboratory Adverse Events

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

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharma Holdings, Inc. at 1(844) 874-7464 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Occasional incidents of acute overdosage of nitrofurantoin oral suspension have not resulted in any specific symptoms other than 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. It is dialyzable.

DOSAGE AND ADMINISTRATION

Nitrofurantoin oral suspension should be given with food to improve drug absorption and, in some patients, tolerance.

Adults

50 to 100 mg four times a day -- the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of nitrofurantoin oral suspension (25 mg/5 mL) for pediatric patients.

Table 3: Pediatric Dosing Table

Weight in Kilograms (kg)	Pediatric Doses (milliliters) and Frequency
7 kg to 11 kg	2.5 mL Four times Daily
12 kg to 21 kg	5 mL Four times Daily
22 kg to 30 kg	7.5 mL Four times Daily
31 kg to 41 kg	10 mL Four times Daily
42 kg or greater	See Adult Dose

Therapy should be continued 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 adults, a reduction of dosage to 50 to 100 mg at bedtime may be adequate. 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 SECTION REGARDING RISKS ASSOCIATED WITH LONG TERM THERAPY**.

HOW SUPPLIED

Nitrofurantoin Oral Suspension USP, 25 mg/5 mL is a yellow color, flavored homogenous suspension free of lumps or aggregates, available in:

Bottle of 230 mL NDC 64980-593-24

Avoid exposure to strong light which may darken the drug. It is stable when stored between 20° to 25°C (68° to 77°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.

Distributed by:
Rising Pharma Holdings, Inc.
East Brunswick, NJ 08816

Made in India

Code: AP/DRUGS/04/2016
Issued: 07/2023

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 25 mg/5 mL (230 mL Container

Label)

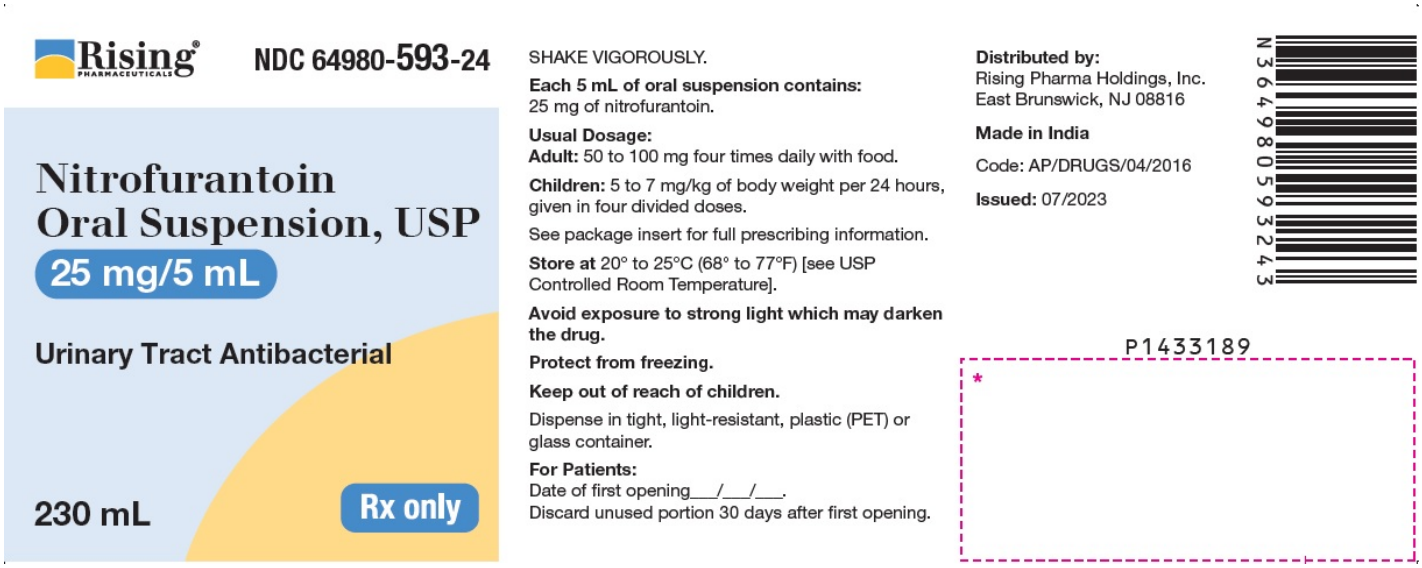
NDC 64980-593-24

Nitrofurantoin Oral Suspension, USP
25 mg/5 mL

Rising Pharma Holdings, Inc. 230 mL

Urinary Tract Antibacterial

Rx only



PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 25 mg/5mL (230 mL Carton Label)

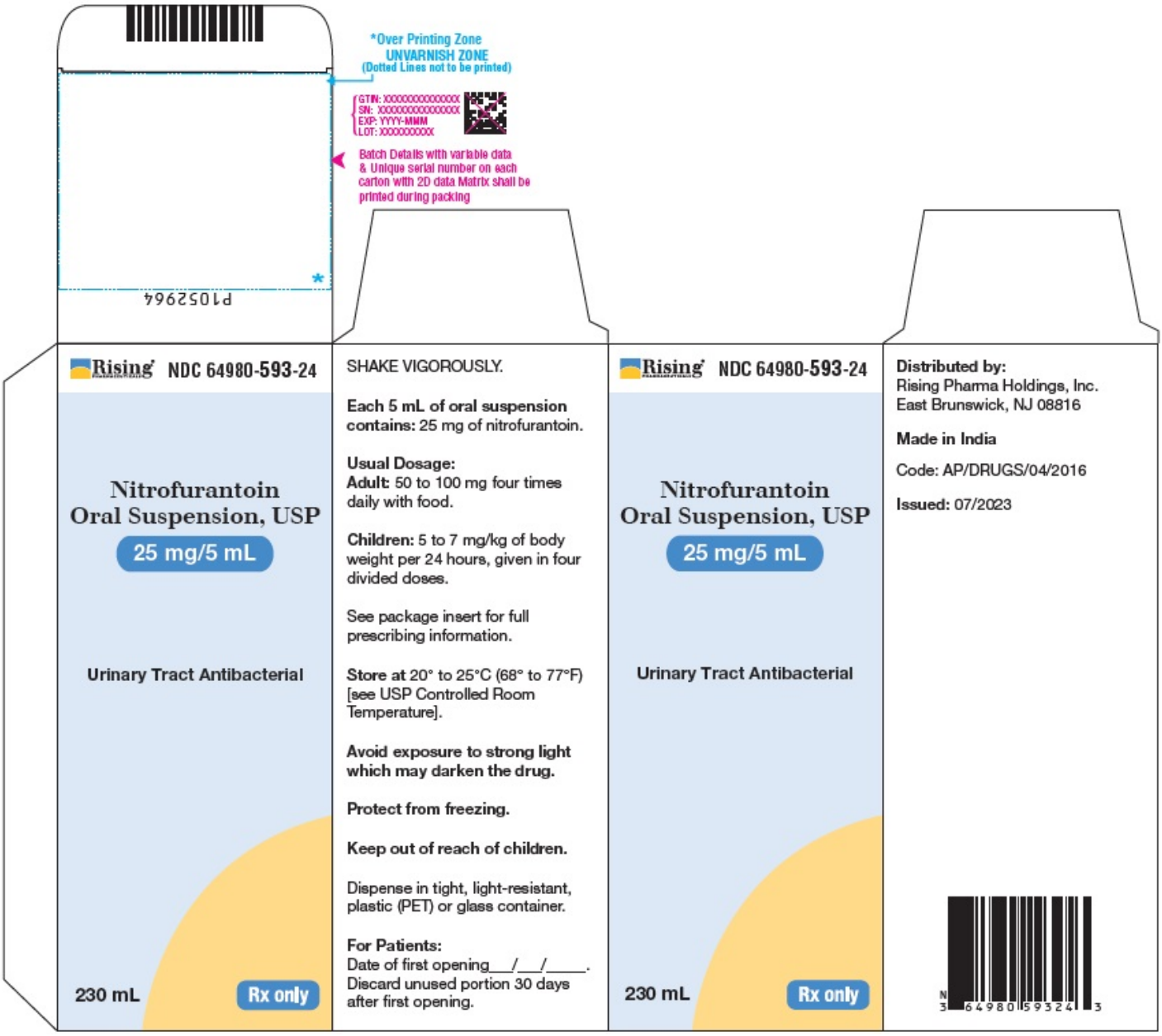
NDC 64980-593-24

Nitrofurantoin Oral Suspension, USP
25 mg/5 mL

Rising Pharma Holdings, Inc. 230 mL

Urinary Tract Antibacterial

Rx only



NITROFURANTOIN

nitrofurantoin suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:64980-593
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NITROFURANTOIN MONOHYDRATE (UNII: E1QI2CQQ1I) (NITROFURANTOIN - UNII:927AH8112L)	NITROFURANTOIN	25 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
BANANA (UNII: 4AJZ4765R9)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED (UNII: K679OBS311)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
GLYCERIN (UNII: PDC6A3C0OX)	
MAGNESIUM ALUMINUM SILICATE TYPE IC (UNII: XLI9KNX1FT)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
MINT (UNII: FV98Z8GITP)	
NONCRYSTALLIZING SORBITOL SOLUTION (UNII: 9E0S3UM200)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
WATER (UNII: 059QF0KO0R)	
SODIUM CITRATE, UNSPECIFIED FORM (UNII: 1Q73Q2JULR)	

Product Characteristics

Color	YELLOW	**Score**	
Shape		**Size**	
Flavor	BANANA, MINT	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64980-593-24	1 in 1 CARTON	05/11/2023	
1		230 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA212607	05/11/2023	

Labeler - Rising Pharma Holdings, Inc. (116880195)

Registrant - Aurobindo Pharma Limited (650082092)

Establishment

Name	Address	ID/FEI	Business Operations
Fabbrica Italiana Sintetici S.p.A,		431189117	API MANUFACTURE(64980-593)

Establishment

Name	Address	ID/FEI	Business Operations
APL HEALTHCARE LIMITED		650918514	ANALYSIS(64980-593) , MANUFACTURE(64980-593)