

PRODUCT MONOGRAPH

Pr AURO-NITROFURANTOIN BID

Nitrofurantoin Capsules USP

(nitrofurantoin monohydrate/macrocrystals)

100 mg

Urinary Tract Antibacterial

Auro Pharma Inc.

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NAME OF DRUG

Pr AURO-NITROFURANTOIN BID
Nitrofurantoin Capsules USP
(nitrofurantoin monohydrate/macrocrystals)

THERAPEUTIC CLASSIFICATION

Urinary Tract Antibacterial

ACTIONS AND CLINICAL PHARMACOLOGY

Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. The broad-based nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria.

Each AURO-NITROFURANTOIN BID (nitrofurantoin capsules) capsule contains two forms of nitrofurantoin. Twenty-five percent is macrocrystalline nitrofurantoin, which has slower dissolution and absorption than nitrofurantoin monohydrate. The remaining 75% is nitrofurantoin monohydrate contained in a tablet form which, upon exposure to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time.

Following a single 100 mg dose, the extent and rate of nitrofurantoin excretion in the urine are similar for 100 mg capsules of nitrofurantoin monohydrate/macrocrystals and 50 or 100 mg capsules of nitrofurantoin macrocrystals. Nitrofurantoin bioavailability can be increased by as much as 40% when nitrofurantoin monohydrate/macrocrystals is administered with food. Approximately 20-25% of a single dose of nitrofurantoin monohydrate/macrocrystals is recovered in the urine unchanged over 24 hours and drug concentrations inhibitory of bacterial growth are reached or exceeded in the urine. Plasma levels attained with nitrofurantoin monohydrate/macrocrystals usually do not exceed 1 mcg/mL and are not considered systemically therapeutic.

Comparative Bioavailability

A double blind, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose oral bioequivalence study of AURO-NITROFURANTOIN BID capsules 100 mg [Test; Aurobindo Pharma Limited, India manufactured for Auro Pharma Inc. (Canada)] verses ^{Pr}MacroBID[®] (Nitrofurantoin Capsules, USP 100 mg [Reference; Allergan Pharma Co.] Canada in 60 healthy, adult, male human subjects under fed conditions.

A summary of the bioavailability data of the 51 subjects who completed the study is presented in

the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Nitrofurantoin (1 X 100 mg Nitrofurantoin Capsule) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (hr. ng/mL)	2007.8 2150.9 (37.0)	1884.3 1999.9 (37.3)	106.6	99.8-113.8
AUC_{0-∞} (hr. ng/mL)	2021.1 2071.8 (31.4)	1830.4 1899.6 (31.4)	110.4%	102.3%-119.2%
C_{max} (ng/mL)	508.8 560.6 (42.3)	411.6 454.9 (44.6)	123.6	111.5-137.0
T_{max}‡ (hr)	7.0 (4.0-24.0)	8.0 (3.0-24.0)		
t_{1/2}§ (hr)	1.0 (42.7)	1.2 (59.0)		

* AURO-NITROFURANTOIN BID (Nitrofurantoin) Capsules 100 mg (Auro Pharma Inc.)

† MacroBID® (Nitrofurantoin) Capsules 100 mg (Reference: Allergan Pharma Co., Canada) were purchased in Canada.

‡ Expressed as the median (range) only.

§ Expressed as arithmetic mean (% CV) only

INDICATIONS AND CLINICAL USE

AURO-NITROFURANTOIN BID is indicated for the treatment of acute uncomplicated urinary tract infections, e.g. cystitis, when due to susceptible strains of *Escherichia coli*, and *Staphylococcus saprophyticus*.

AURO-NITROFURANTOIN BID is not indicated for the treatment of associated renal cortical or perinephric abscesses.

AURO-NITROFURANTOIN BID is not indicated for therapy of any systemic infections or for use in prostatitis.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AURO-NITROFURANTOIN BID and other antibacterial drugs, AURO-NITROFURANTOIN BID should be used only to treat 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.

CONTRAINDICATIONS

Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients during labour and delivery, or when the onset of labour is imminent, and in infants under one month of age because of the possibility of hemolytic anemia in the fetus or the newborn infant due to their immature erythrocyte enzyme systems (glutathione instability).

AURO-NITROFURANTOIN BID capsule therapy is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

WARNINGS

Acute, subacute or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin products (SEE ADVERSE REACTIONS). If these reactions occur, the drug should be withdrawn 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 ADVERSE REACTIONS).

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

Peripheral neuropathy (including optic neuritis) may occur with nitrofurantoin therapy; this may become severe or irreversible. Fatalities have been reported. Predisposing 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 such occurrence. Patients receiving long-term therapy should be monitored periodically for changes in renal function. If numbness or tingling occurs, discontinue use.

Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. The 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. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn.

Pseudomonas is the organism most commonly implicated in superinfections in patients with nitrofurantoin preparations.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Nitrofurantoin presented evidence of carcinogenic activity in female B₆C₃F₁ mice as shown by increased incidences of tubular adenomas, benign mixed tumours, and granulosa cell tumours 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 three subcutaneous injections of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas were observed in the F1 generation.

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 BDF₁ mice revealed no evidence of carcinogenicity.

Nitrofurantoin has demonstrated mutagenic potential in a variety of laboratory assays conducted *in vitro* with mammalian and non-mammalian cells exposed to therapeutically attainable and higher concentrations. Point and possibly other types of mutations were observed in bacteria, yeast and fungi. Damage to DNA or inhibition of DNA synthesis were produced in human fibroblasts and lymphocytes, and Chinese hamster ovaries and lung fibroblasts.

In vivo tests on rodents utilizing a wide range of doses demonstrated similar potential. DNA damage to liver, lung, spleen and kidney were observed in rat (alkaline elution test), immature red blood cells (rat micronucleus test) and sperm (H-test in mouse). Some test results were negative such as the sex-linked recessive lethal assay in *Drosophila* where nitrofurantoin was administered by feeding or injection.

The significance of the carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown. Because of the potential toxicity of nitrofurantoin when used for long-term therapy, the benefits of long-term therapy should be weighed against potential risks (See DOSAGE AND ADMINISTRATION section for prescribing information).

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

Susceptibility/Resistance:

Development of Drug Resistant Bacteria:

Prescribing AURO-NITROFURANTOIN BID in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

PRECAUTIONS

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 drug onto the surface of magnesium trisilicate. Nitrofurantoin should not be given along with drugs which may produce impaired renal function. Uricosuric drugs, such as probenecid and sulfinpyrazone, may inhibit renal tubular secretion of nitrofurantoin. The resulting increase in 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 administration of nitrofurantoin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solution but not with the glucose enzymatic test.

Antimicrobial Antagonism:

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobials. Although the clinical significance of this finding is unknown, concomitant AURO-NITROFURANTOIN BID and quinolone therapy should be approached with caution.

Pregnancy:

Several reproduction studies performed in rabbits and rats with low multiples of human doses and plasma levels revealed no evidence of general reproductive effects, impaired fertility or harm to the fetus. However, in one published study in which pregnant mice were administered 250 mg/kg subcutaneously on three days, growth retardation and a low incidence of malformations were observed. These effects were not observed at 100 mg/kg. In another controlled study in which cultured rat embryos were exposed for 26 hours to concentrations of 48 mcg/mL all were malformed. None of those exposed to 60 mcg/mL of nitrofurantoin survived.

The relevance of these findings to humans is uncertain. There are, however, no adequate well controlled studies in pregnant women. Though animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless clearly

needed.

Labour and Delivery:

Nitrofurantoin should not be given to women during labour and delivery, or when the onset of labour is imminent (SEE CONTRAINDICATIONS).

Nursing Mothers:

Nitrofurantoin has been detected in trace amounts in breast milk. Caution should be exercised when nitrofurantoin is administered to a nursing woman, especially if the infant is known or suspected to have a glucose-6-phosphate dehydrogenase deficiency (SEE CONTRAINDICATIONS).

Pediatric Use:

Nitrofurantoin is contraindicated in infants under one month of age (SEE CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

In limited clinical trials, nitrofurantoin monohydrate/macrocrystals 100 mg capsule b.i.d. demonstrated an equivalent side effect profile to nitrofurantoin macrocrystals 50 mg q.i.d.

In clinical trials of nitrofurantoin monohydrate/macrocrystals the most frequent clinical adverse events that were reported as possibly or probably drug-related were nausea (8%), headache (6%), and flatulence (1.5%).

The following additional clinical adverse events have been reported with the use of nitrofurantoin:

Respiratory:

Chronic, subacute or acute pulmonary hypersensitivity reactions may occur with the use of nitrofurantoin (SEE WARNINGS). Chronic pulmonary reactions generally occur in patients who have received continuous treatment for 6 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 the degree of their 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 nitrofurantoin therapy. The risk is greater when 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 is not stopped, the symptoms may become more severe.

Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or 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 ECG may occur associated with pulmonary reactions.

Collapse and cyanosis have seldom been reported.

Gastrointestinal:

Diarrhea, dyspepsia, abdominal pain, constipation, emesis, sialadenitis, pancreatitis.

Pseudomembranous colitis, including that due to an overgrowth by *Colstridium difficile*, have been reported rarely with the use of nitrofurantoin.

Hepatic:

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis occur rarely (SEE WARNINGS).

Neurologic:

Peripheral neuropathy, including optic neuritis (SEE WARNINGS).

Dizziness, drowsiness, amblyopia, asthenia, vertigo, and nystagmus also have been reported with the use of nitrofurantoin.

Benign intracranial hypertension has seldom been reported.

Confusion, depression, euphoria and psychotic reactions have been reported rarely.

Dermatologic:

Alopecia.

Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome) have been reported rarely.

Allergic Reactions:

Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous or eczematous eruptions; pruritis; urticaria; anaphylaxis; arthralgia; myalgia; drug fever; chills; and malaise have been reported.

Hematologic:

Glucose-6-phosphate dehydrogenase deficiency anemia (SEE WARNINGS), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia, and eosinophilia have occurred. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

Miscellaneous:

As with other antimicrobial agents, superinfections with resistant organisms, e.g., *Pseudomonas* species or *Candida* species, may occur with the use of nitrofurantoin. Superinfections have been limited to the genitourinary tract.

Increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin and increased serum phosphorus.

Nitrofurantoin may cause a rust yellow to brown discolouration of the urine. The clinical significance is unknown.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptomatology other than vomiting. In case vomiting does not occur soon after an excessive dose, induction of emesis is recommended. There is no specific antidote for nitrofurantoin but a high fluid intake should be maintained to promote urinary excretion of the drug. It is dialyzable.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Adults and Children over 12 years:

One AURO-NITROFURANTOIN BID 100 mg capsule twice a day for 7 days (maximum 200 mg/day).

AURO-NITROFURANTOIN BID should be taken every 12 hours with food or milk to minimize gastric upset.

Therapy for acute urinary tract infections should be continued for 7 days or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for re-evaluation.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name

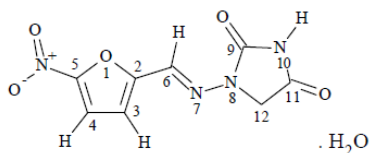
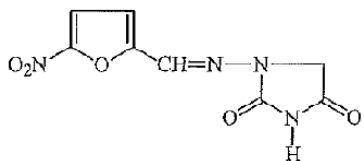
Nitrofurantoin Macrocrystals Nitrofurantoin Monohydrate

Chemical Name

Nitrofurantoin Macrocrystals: 1-[[[5-Nitro-2-furanyl)methylene]amino]2,4-imidazolidinedione.

Nitrofurantoin Monohydrate: 2,4-Imidazolidinedione,1-[[[5-Nitrofuranyl) methylene] amino]- monohydrate

Structural Formula



Molecular Formula



Molecular Weight

238.16 g/mol

256.17 g/mol

Description

Nitrofurantoin Macrocrystals: Lemon-yellow crystals, very slightly soluble in water and alcohol and soluble in dimethylformamide.

Nitrofurantoin Monohydrate: Lemon-yellow, odorless crystals or fine powder Soluble in Dimethyl formamide.

Storage

Store at room temperature (15°C to 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form	Capsules
Strength	100 mg
Description	Opaque black and opaque yellow size '0' hard gelatin capsule imprinted with 'Z' on cap and '100' on body with grey ink filled with light yellow to yellow powder and one yellow colored, round, biconvex tablet.
Composition	<p>Each Nitrofurantoin USP 100 mg capsule contains 25 mg of Nitrofurantoin in the form of Nitrofurantoin macrocrystals & 75 mg of Nitrofurantoin monohydrate.</p> <p>Lactose Monohydrate, Corn starch, Carbomer 934 P (Carbopol 974 P NF), Carbomer 941 (Carbopol 971 P), Povidone, Compressible sugar, Talc and Magnesium stearate.</p> <p>Capsule Shell Ingredients: FD&C Blue 1, FD&C Red 40, Gelatin, Titanium Dioxide, D&C Yellow 10, Sodium Lauryl Sulfate.</p> <p>Printing ink Ingredients: Shellac NF, Potassium hydroxide NF, Titanium dioxide USP E171, Black Iron Oxide NF E172.</p> <p>Complies to USP Dissolution Test 3.</p>
Packaging	HDPE bottles of 100's, 500's and 1000's capsules.

MICROBIOLOGY

The *in vitro* antibacterial activity of nitrofurantoin against clinical isolates is given below.

Organism (# strains tested)	Minimal Inhibitory Concentration (mcg/mL)		
	MIC ₅₀	MIC ₉₀	Range
<i>Citrobacter freundii</i> (97)	32	32	16 - >128
<i>Enterobacter aerogenes</i> (75)	64	128	32 - 128
<i>Enterobacter cloacae</i> (135)	64	128	4 - 128
<i>Escherichia coli</i> (1792)	16	32	8 - 128
<i>Klebsiella oxytoca</i> (52)	32	64	≤16 - >128
<i>Klebsiella pneumoniae</i> (410)	64	128	32 - >128
<i>Staphylococcus aureus</i> (84)	16	32	16 - 32
<i>Staphylococcus epidermidis</i> (25)	16	16	8 - 32
<i>Staphylococcus saprophyticus</i> (25)	16	16	8 - 32
<i>Enterococcus faecalis</i> (598)	16	16	8 - 64

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

Nitrofurantoin is bactericidal in urine at levels equal to one or two times the MIC. Nitrofurantoin exhibits concentration dependent killing of bacteria.

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobials. The clinical significance of this finding is unknown.

Development of resistance to nitrofurantoin has not been a significant problem since its introduction in 1953. Cross-resistance with antibiotics and sulfonamides has not been observed, and transferable resistance is, at most, a very rare phenomenon.

Susceptibility Tests - Quantitative methods that require measurement of zone diameters give the most precise estimates of antimicrobial susceptibility. One recommended procedure, (National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disc Susceptibility Tests, Approved Standard: M2- A4, Vol. 10, Number 7, 1990), uses a disc containing 300 mcg nitrofurantoin for testing susceptibility.

Reports from the laboratory should be interpreted according to the following criteria:

Susceptible organisms produce zones of 17 mm or greater indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15 to 16 mm, indicating that the tested organism may or may not be susceptible.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Alternatively, a bacterial isolate may be considered susceptible if the MIC value for nitrofurantoin is not more than 32 mcg/mL. A MIC of 64 mcg/mL indicates intermediate susceptibility. Organisms are considered resistant if the MIC is equal to or greater than 128 mcg/mL.

Dilution and diffusion susceptibility tests should give MICs and zone diameters within the ranges listed below for the following quality control organisms.

Organism	MIC (mcg/mL)	Zone Size Range (mm)
<i>E. coli</i> (ATCC 25922)	4-16	20-25
<i>S. aureus</i> (ATCC 29213)	8-32	18-22
<i>E. faecalis</i> (ATCC 29212)	4-16	- -

PHARMACOLOGY

Human:

Nitrofurantoin taken orally is rapidly absorbed from the gastrointestinal tract and appears to be widely distributed. Based upon urine recovery levels its bioavailability may be increased by as much as 40% when administered with food. In one study in which healthy male adults were provided a single 100 mg capsule of nitrofurantoin monohydrate/macrocrystals with food the C_{max} , t_{max} , AUC and elimination $t_{1/2}$ were respectively 0.6 mcg/mL, 5 hrs and 1.8 mcg/mL x hrs and 0.8 hrs in plasma. In urine C_{max} , t_{max} and elimination $t_{1/2}$ were respectively 144 mcg/mL, 5.1 hrs and 1.1 hrs. Plasma levels do not normally exceed 1 mcg/mL following therapeutic administration of Nitrofurantoin monohydrate/macrocrystals to subjects with normal kidney function. Levels far exceeding those in plasma have been reported for human bile, seminal fluid and kidney. About 20-25% of a single dose of nitrofurantoin monohydrate/macrocrystals is recovered in the urine and about 1.5% of urine contents are metabolized. Little is known about nitrofurantoin metabolism and the rate or extent of its excretion by other routes in humans.

Animal:

In Sprague-Dawley rats nitrofurantoin was rapidly and completely absorbed from the gastrointestinal tract and was widely distributed. Following administration of 0.5 mg/kg of a suspension by gavage it was excreted primarily in the feces (58%, all of which was metabolized) and urine (35%, three quarters of which was metabolized). A C_{max} of 0.05 mcg/mL was attained at 0.5 hrs. Admixed to food in long term toxicity studies at average doses of 96 mg/kg/day plasma levels of 0.39 and 1.1 mcg/mL were recorded in males and females respectively. The maximal plasma levels attained in rats appear low relative to those attained in humans.

TOXICOLOGY

Chronic Toxicity and Carcinogenicity Studies:

Nitrofurantoin was not considered carcinogenic when administered for 22 months to male and female Swiss mice at dietary doses up to 181 and 224 mg/kg/day respectively and in male and female BDF₁ mice at dietary doses (estimated from feed consumption of Swiss and B₆C₃F₁ mice historical controls) of up to 550 and 560 mg/kg/day respectively for 24 months. There was an increase in mortality in the high dosed males and changes in the urinary system and gonads (increase in ovarian cysts and testicular degeneration/atrophy) observed in Swiss mice. No neoplastic lesions were attributed to the administration of nitrofurantoin for either strain of mouse.

In a chronic study, nitrofurantoin was consumed in the diet for two years by male and female Sprague-Dawley rats in doses of up to 81 and 116 mg/kg/day respectively. In a carcinogenicity study Sprague-Dawley male and female rats consumed dietary nitrofurantoin for 2 years in doses of up to 43 and 56 mg/kg/day respectively. No evidence of carcinogenicity was observed in these

studies. In the higher dose groups, increased mortality, testicular degeneration, epididymal fibrosis and sciatic nerve fibrosis was seen in males and an increase in bile duct hyperplasia and sciatic nerve demyelination was seen in females.

In a large carcinogenicity study conducted by the U.S. Department of Health and Human Services F344/N rats consumed dietary nitrofurantoin for 2 years in average amounts equivalent to 59 or 111 mg/kg/day for males and 29 or 62 mg/kg/day for females. B₆C₃F₁ mice consumed dietary nitrofurantoin for 2 years in average amounts equivalent to 295 or 567 mg/kg/day for males and 277 or 577 mg/kg/day for females. Evidence of tumorigenicity and carcinogenicity was noted.

(SEE WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility:

(SEE WARNINGS)

General Reproductive Studies:

(SEE PRECAUTIONS)

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**PrAURO-NITROFURANTOIN BID
Nitrofurantoin Capsules USP
(nitrofurantoin monohydrate/macrocrystals)**

Read this carefully before you start taking **AURO-NITROFURANTOIN BID** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AURO-NITROFURANTOIN BID**.

What is AURO-NITROFURANTOIN BID used for?

AURO-NITROFURANTOIN BID is used to treat infections of the urinary tract.

Antibacterial drugs like AURO-NITROFURANTOIN BID treat only bacterial infections. They do not treat viral infections.

How does AURO-NITROFURANTOIN BID work?

AURO-NITROFURANTOIN BID is an antibiotic. It is activated when it is broken down by bacteria. After it is activated, AURO-NITROFURANTOIN BID kills bacteria and prevents the growth of infections.

What are the ingredients in AURO-NITROFURANTOIN BID?

Medicinal ingredient: Nitrofurantoin

Non-medicinal ingredients: Lactose Monohydrate, Corn starch, Carbomer 934 P (Carbopol 974 P NF), Carbomer 941 (Carbopol 971 P), Povidone, Compressible sugar, Talc and Magnesium stearate.

Capsule Shell Ingredients: FD&C Blue 1, FD&C Red 40, Gelatin, Titanium Dioxide, D&C Yellow 10, Sodium Lauryl Sulfate. Printing ink Ingredients: Shellac NF, Potassium hydroxide NF, Titanium dioxide USP E171, Black Iron Oxide NF E172.

AURO-NITROFURANTOIN BID comes in the following dosage forms:

AURO-NITROFURANTOIN BID is available as a 100 mg capsule.

Do not use AURO-NITROFURANTOIN BID if:

- you are allergic to any ingredient in AURO-NITROFURANTOIN BID. Make sure to read “What are the ingredients in AURO-NITROFURANTOIN BID?” above.
- you have a severe disease of the kidneys.
- you are in the final stages of pregnancy (in labour or during delivery) as there is a risk that it might affect the baby

Do not give AURO-NITROFURANTOIN BID to newborns or infants under one month of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AURO-NITROFURANTOIN BID. Talk about any health conditions or problems you may have, including if you:

- have disease of the lungs. You may develop lung disease if you need to take AURO-NITROFURANTOIN BID for a number of months. Your doctor must regularly check how your lungs are working. Talk to your doctor about benefits and risks of taking AURO-NITROFURANTOIN BID for a long term.
- have liver disease. Your doctor may want to regularly check how your liver is working. Your doctor may want to regularly check how your liver is working. If you get liver disease while taking AURO-NITROFURANTOIN BID, you should immediately stop taking the medicine and talk to your doctor.
- have kidney disease

- lack an enzyme (body chemical) called G6PD (glucose-6-phosphate dehydrogenase). Your red blood cells are more easily damaged if you do not have this enzyme. This condition is more common in black people and people of Mediterranean or near- Eastern origin. Your doctor will know about this.
- Are breast feeding a baby with suspected or known deficiency in an enzyme called G6PD (glucose-6-phosphate dehydrogenase).
- Are pregnant or are planning to become pregnant.

Other warnings you should know about:

- The following conditions may increase the chance of developing a side effect which causes damage to the nerves, altered sense of feeling, like pins and needles:
 - anaemia (a decrease in red blood cells causing pale skin, weakness and breathlessness);
 - diabetes
 - a lack of vitamin B
 - abnormal levels of salts in your blood.
 - you are suffering from an illness that makes you very tired

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AURO-NITROFURANTOIN BID:

Medicines:

- medicines for indigestion (Antacids e.g. magnesium trisilicate)
- medicines for gout (e.g. probenecid or sulfinpyrazone)

You should not take AURO-NITROFURANTOIN BID along with medicines that affect your kidneys

Laboratory tests:

- If you are taking AURO-NITROFURANTOIN BID, you may get false positive results when you test your urine for sugars (glucose).

How to take AURO-NITROFURANTOIN BID:

- AURO-NITROFURANTOIN BID should be taken every 12 hours with food or milk. This will help to avoid upset stomach.
- Although you may feel better early in treatment, AURO-NITROFURANTOIN BID should be used exactly as directed.
- Misuse or overuse of AURO-NITROFURANTOIN BID could lead to the growth of bacteria that will not be killed by AURO-NITROFURANTOIN BID (resistance). This means that AURO-NITROFURANTOIN BID may not work for you in the future.
- Do not share your medicine.

Usual dose:

Adults and Children over 12 years:

One AURO-NITROFURANTOIN BID 100 mg capsule twice a day for 7 days. Do not take more than 2 capsules per day.

If you have a urinary tract infection, your doctor will decide how long you should take AURO-NITROFURANTOIN BID.

Overdose:

If you think you have taken too much AURO-NITROFURANTOIN BID, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take AURO-NITROFURANTOIN BID, do not worry. If you remember later on that day, take that day’s dose as usual. If you miss a whole day’s dose take the normal dose on the next day. Do not take a double dose to make up for a forgotten capsule. If you are not sure ask your doctor or pharmacist.

What are possible side effects from using AURO-NITROFURANTOIN BID?

These are not all the possible side effects you may feel when taking AURO-NITROFURANTOIN BID. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects in people who take AURO-NITROFURANTOIN BID include:

- nausea or vomiting
- headache
- flatulence (passing gas)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
• Lung disease (May include fever, chills, cough, chest pain and shortness of breath)			√
• Liver problems (skin and eyes appear yellowish, itchy skin, dark urine color)			√
• Numbness or tingling			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C-30°C).
Keep out of reach and sight of children.

If you want more information about AURO-NITROFURANTOIN BID:

- Talk to your healthcare professional

- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website [http:// www.auopharma.ca](http://www.auopharma.ca), or by calling 1-855-648-6681.

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