PRODUCT MONOGRAPH

[Pr]JAMP NITROFURANTOIN

Nitrofurantoin Macrocrystals Capsules

50 and 100 mg

House Standard

Urinary Tract Antibacterial

JAMP Pharma Corporation
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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.

Jamp Nitrofurantoin (nitrofurantoin macro crystals) is a larger crystal form of nitrofurantoin. The absorption of nitrofurantoin macro crystals is slower and its urinary excretion is somewhat less when compared to nitrofurantoin tablets. At therapeutic doses, low drug concentrations are observed in blood, with therapeutic concentrations achieved only in the urine. A number of patients who cannot tolerate nitrofurantoin tablets can take nitrofurantoin capsules without nausea.

Comparative Bioavailability Studies

A double-blind, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Jamp Nitrofurantoin capsules, 100 mg (JAMP Pharma Corporation) and [Pr]TEVA-NITROFURANTOIN capsules, 100 mg (Teva Canada Limited) was conducted in 24 healthy adult human subjects under fed conditions. The summary data are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Nitrofurantoin (1 x 100 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (hr*ng/mL)	2469.00 2506.08 (17.58)	2337.31 2386.84 (21.17)	105.6	100.2 - 111.4
AUC_I (hr*ng/mL)	2508.29 2545.35 (17.43)	2420.73 2467.94 (20.23)	103.6	98.5 - 109.0
C_{max} (ng/mL)	469.91 479.66 (22.23)	462.99 484.12 (31.91)	101.5	94.5 - 109.0
T_{max}§ (hr)	4.67 (2.50 - 6.50)	5.00 (4.33 - 7.00)		
$T_{½}$€ (hr)	1.38 (42.85)	1.63 (66.17)		

* Jamp Nitrofurantoin capsules, 100 mg (JAMP Pharma Corporation).
† [Pr]TEVA-NITROFURANTOIN capsules, 100 mg (Teva Canada Limited) were purchased in Canada.
§ Expressed as the median (range) only.
€Expressed as arithmetic mean (CV%) only.

INDICATIONS AND CLINICAL USE

Jamp Nitrofurantoin is indicated for the treatment of urinary tract infections, e.g., cystitis, when due to susceptible strains of *E. coli, enterococci,* S. *aureus* and certain susceptible strains of *Klebsiella* species, *Enterobacter* species, and *Proteus* species.

It is not indicated for treatment of associated renal cortical or perinephric abscesses.

Nitrofurantoin 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 Jamp

Nitrofurantoin and other antibacterial drugs, Jamp Nitrofurantoin 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

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with Jamp Nitrofurantoin 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 Jamp Nitrofurantoin, other therapeutic agents with broader tissue distribution should be selected. In considering the use of Jamp Nitrofurantoin, 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 to therapy with this drug. Treatment in these patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, the drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients during labour and delivery, or when the onset of labor 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).

Jamp Nitrofurantoin is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

WARNINGS

Acute, subacute and 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% 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 $B_6C_3F_1$ mice as shown by increased incidences of tubular adenomas, benign mixed tumor and granulosa cell tumor 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 2 chronic bioassays in Swiss mice and BDF_1 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 was 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 Drosophilia 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 Jamp Nitrofurantoin 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.

Clostridium difficile-associated diarrhea: *Clostridium 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 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

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. Jamp 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 Jamp Nitrofurantoin and quinolone therapy should be approached with caution.

Pregnancy:

Pregnancy Category B

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 3 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:

Jamp Nitrofurantoin should not be given to women during labor and delivery, or when the onset of labor 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: Jamp Nitrofurantoin is contraindicated in infants under one month of age. (See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Geriatric Use: Clinical studies of nitrofurantoin macrocrystal formulations did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Spontaneous reports suggest a higher proportion of pulmonary reactions, including fatalities, in elderly patients; these differences appear to be related to the higher proportion of elderly patients receiving long-term nitrofurantoin therapy. As in younger patients, chronic pulmonary reactions generally are observed in patients receiving therapy for six months or longer (see WARNINGS). Spontaneous reports also suggest an increased proportion of severe hepatic reactions, including fatalities, in elderly patients (see WARNINGS).

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy should be considered when prescribing Jamp Nitrofurantoin. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications (see CONTRAINDICATIONS). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Information for Patients: Patients should be advised to take Jamp Nitrofurantoin 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 occur during therapy.
Many patients who cannot tolerate microcrystalline nitrofurantoin are able to take Jamp Nitrofurantoin without nausea.

ADVERSE REACTIONS

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 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 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 colititis, including that due to an overgrowth by *Clostridium 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 reaction 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. Nitrofurantoin is dialyzable.

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

DOSAGE AND ADMINISTRATION

Adults: 50-100 mg four times a day.

Children: Dosage should be calculated on the basis of 5-7 mg/kg of body weight per 24 hours given in divided doses four times a day (contraindicated in infants under one month).

Jamp Nitrofurantoin may be given with food or milk to further minimize gastric upset.

Therapy should be continued for at least one week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for re-evaluation.

For long-term suppressive therapy in adults, a reduction of dosage to 50-100 mg once daily at bedtime may be adequate. See WARNINGS section regarding risks associated with long-term therapy. For long-term suppressive therapy in children, doses as low as 1 mg/kg/24 hours, given in a single or in two divided doses, may be adequate.

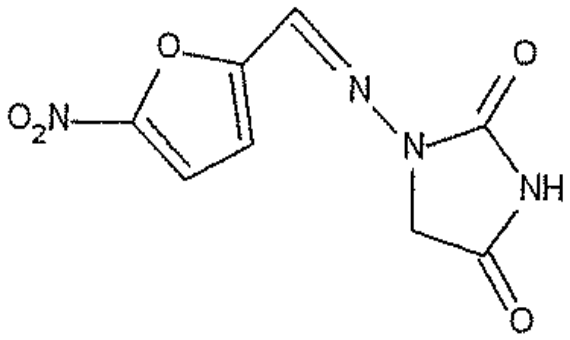
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Nitrofurantoin Macrocrystals

Chemical Name: 2,4-Imidazolidinedione, 1-[[(5-nitro-2-furanyl)methylene]amino]-

Structural Formula:



Molecular Formula: $C_8H_6N_4O_5$ Molecular Weight: 238.16 g/mol

Description: Lemon-yellow crystalline powder; very slightly soluble in water and in alcohol and soluble in dimethylformamide.

STABILITY AND STORAGE RECOMMENDATION

Store between 15° - 30°C.

Composition:

50 mg Capsules: Lactose Monohydrate, Maize Starch, talc. The capsule shell contains Quinoline Yellow, gelatin, titanium dioxide. Printing Material composition: Shellac, Propylene Glycol, Black Iron Oxide and Potassium Hydroxide.

100 mg Capsules: Lactose Monohydrate, Maize starch, talc. The capsule shell contains Quinoline Yellow, gelatin, titanium dioxide. Printing Material composition: Shellac, Propylene Glycol, Black Iron Oxide and Potassium Hydroxide.

AVAILABILITY OF DOSAGE FORMS

Jamp Nitrofurantoin is available as:

50mg- Pale yellow to yellow granular powder in yellow opaque cap and white opaque body, size #2 hard gelatin capsules. Printed in black **NF 50** on cap and body of the capsule**.**

100 mg- Pale yellow to yellow granular powder in yellow opaque cap and yellow opaque body, size #2 hard gelatin capsules. Printed in black **NF 100** on body and cap of the capsule.

Supplied in bottles of 500 and 1000 capsules.

MICROBIOLOGY

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

	Minimal Inhibitory Concentration (mcg/mL)		
Organism (# strains tested)	**MIC_{50}**	**MIC_{90}**	**Range**
Citrobacter freundii (97)	32	32	16 - >128

Enterobacter aerogenes (75)	64	128	32 – 128
Enterobacter cloacae (135)	64	128	4 – 128
Escherichia coli (1792)	16	32	8 – 128
Klebsiella oxytoca (52)	32	64	≤16 - >128
Klebsiella pneumoniae (410)	64	128	32 - >128
Staphylococcus aureus (84)	16	32	16 – 32
Staphylococcus epidermidis (25)	16	16	8 – 32
Staphylococcus saprophyticus (25)	16	16	8 – 32
Enterococcus faecalis (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)
E. coli (ATCC 25922)	4-16	20-25
S. aureus (ATCC 29213)	8-32	18-22
E. faecalis (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 with food, the C_{max}, t_{max}, and elimination t1/2 were respectively 100 mcg/mL, 3.6 hrs and 1.13 hrs in urine. Plasma levels do not normally exceed 1 mcg/mL following therapeutic administration of nitrofurantoin 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 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 BDF_1 mice at dietary doses (estimated from feed consumption of Swiss and $B_6C_3F_1$ 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-Da wley 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. $B_6C_3F_1$ 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)

BIBLIOGRAPHY

1. Hailey, F.J. and Glascock, H.W. Jr. Gastrointestinal Tolerance to a New Macrocrystalline Form of Nitrofurantoin: A Collaborative Study. Current Ther. Res. 1967 9:600.
2. Sachs, J., Geer, T., Noell, P., Kunn, C.M. Effect of Renal Function on Recovery of Orally Administered Nitrofurantoin. New Eng. J. Med. 1968 278:1032-1035.
3. Goff, J.B., Schlegel, J.U., O'Dell, R.M. Urinary Excretion of Nalidixic Acid, Sulfamethizole, and Nitrofurantoin in Patients with Reduced Renal Function. J. Urol. 1968 99:371-375.
4. Beutler, E. The Hemolytic Effect of Primaquine and Related Compounds: A Review. Blood 1959 14:103-109.
5. Gross, R.T. and Hurwitz, R.E. The Pentose Phosphate Pathway In Human Erythrocytes; Relationship Between the Age of the Subject and Enzyme Activity. Pediatrics 1958 22:453-460.
6. Zinkham, W.H., An in vitro Abnormality of Glutathione Metabolism in Erythrocytes from Normal Newborns: Mechanism and Clinical Significance. Pediatrics 1959 23:18-32.
7. Burka, E.R., Weaver, Z. III, and Marks, P.A. Clinical Spectrum of Hemolytic Anemia Associated with Glucose-6-Phosphate Dehydrogenase Deficiency. Ann. Int. Med. 1966 4:817-825.
8. Alving, R.S., Kellermeyer, R.W., Tarlov, A., Schrier, S., and Carson, P.E. Biochemical and Genetic Aspects of Primaquine Sensitive Hemolytic Anemia. Ann. Int. Med. 1958 49:240-248.
9. Conklin, J.D., Hollifield, R.D. A New Method for the Determination of Nitrofurantoin in Urine. Clin. Chem. 1965 11:925-931.
10. Conklin, J.D., Hollifield, R.D. A Quantitative Procedure for the Determination of Nitrofurantoin in Whole Blood and Plasma. Clin. Chem. 1966 12:690-696.
11. Uesu, C.T. Peripheral Neuropathy Due to Nitrofurantoin: Case Report and Review of the Literature. Ohio State Med. J. 1962 58:53-56.

12. Willett, R.W. Peripheral Neuropathy Due to Nitrofurantoin. Neurology 1963 13:344-345.

13. Paul, H.E., Hayes, K.J., Paul, M.F., and Borgman, A.R. Laboratory Studies with Nitrofurantoin. Relationship Between Crystal Size, Urinary Excretion in the Rat and Man, and Emesis in Dogs. J. Pharm. Sci. 1967 56:882.

14. Conklin, J.D. and Hailey, F.J. Urinary Drug Excretion in Man During Oral Dosage of Different Nitrofurantoin Formulations. Clin. Pharm. and Therap.1969 10:534-539.

15. McOsker, C.C., Pollack, J.A., Andersen, J.A. Inhibition of Bacterial Protein Synthesis by Nitrofurantoin Macrocrystals: An Explanation for the Continued Efficacy of Nitrofurantoin. Management of Urinary Infections, Internat. Congress and Symposium Series No. 154, Proc. Internat. Consensus Conf. Sponsored by Norwich Eaton Pharmaceuticals, Inc., Montreal, Canada, Nov. 11-12, 1988, ed. Harrison, L.H., Royal Society of Medicine Services Ltd., London, 1990, P. 33-44.

16. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disc Susceptibility Tests, Approved Standard: M2-A4, Vol. 10, Number 7, 1990.

17. Butler, W.H., Graham, T.C., and Sutton, M.L. Oncogenicity Study of Macrodantin in Swiss Mice. Food Chem. Toxicol.1990 28(1):49-54.

18. Stitzel, K.A., McConnell, R.F., and Dierckman, T.A. Effects of Nitrofurantoin on the Primary and Secondary Reproductive Organs of Female B6C3F1 Mice. Toxicol. Pathol. 1989 17(4, Part 2):774-781.

19. U.S. Department of Health and Human Services (1989). Toxicology and Carcinogenesis Studies of Nitrofurantoin (CAS No. 67-20-9) in F344/N Rats and B6C3F1 Mice. National Toxicology Program. Technical Report Series No. 341. NIH Publication No. 89-2597.

20. Bignami, M., et al. Non-Disjunction and Crossing-Over Induced by Pharmaceutical Drugs in Apsergillus nidulans. Mut. Res. 1974 26:159-170.

21. Harnasch, D., and Rudolf, S. Studies on the Induction of Histocompatibility Gene Mutations in Germ Cells of Mice by Chemical Mutagens and/or Virus-Inducing Compounds. Mut. Res. 1984 126:279-295.

22. Heddle, J.A., et al. The Induction of Micronuclei as a Measure of Genotoxicity. Mut. Res. 1983 123: 61-118.

23. Hirsch-Kauffman, M., Herrlich, P., and Schweiger, M. Nitrofurantoin Damages DNA of Human Cells. Klin. Wschr 1978 56:405-407.

24. Ishidate, M., Harnois, M.C., and Sofuni, T. A Comparative Analysis of Data on the Clastogenicity of 951 Chemical Substances Tested in Mammalian Cell Cultures. Mut. Res. 1988 195:151-213.

25. Obaseiki-Ebor, E.E., and Akerele, J.O. Nitrofuran Mutagenicity: Induction of Frameshift Mutations. Mut. Res. 1986 175:149-152.

26. Parodi, S., et al. Alkaline DNA Fragmentation, DNA Disentanglement Evaluated Viscosimetrically and Sister Chromatid Exchanges, After Treatment in vivo with Nitrofurantoin. Chem. Biol. Interact. 1983 45:77-94.

27. Russo, P., et al. DNA Damage in Liver of Rats Treated with Nitrofurantoin, Mut. Res.1982 105:377-382.

28. Siebert, D., Bayer, U., and Marquardt, H. The Application of Mitotic Gene Conversion in Saccharomyces cerevisiae in a Pattern of Four Assays, in vitro and in vivo, for Mutagenicity Testing. Mut. Res.1979 67:145-156.

29. Shirai, T., and Wang, C.Y. Enhancement of Sister Chromatid Exchange in Chinese Hamster Ovary Cells by Nitrofurans. Mut. Res. 1980 79:345-350.

30. Mercado, C. et al. Inhibition of T-cell Mitogenesis by Nitrofurans. Biochem. Pharmacol. 1991 41(4): 503.

31. Nomura, T., et al. Induction of Tumors and Malformations in Mice After Prenatal Treatment With Some Antibiotic Drugs. Med. J. Osaka Univer. 1984 35(1-2): 13.

32. Greenaway, J.C., et al. On the Capacity of Nitroheterocyclic Compounds to Elicit an Unusual Axial Symmetry in Cultured Rat Embryos. Toxicol. Applied Pharmacol.1986 82(2): 307.

33. Shah, S. and Greenwood, D. Interactions between antibacterial agents of the quinolone group and nitrofurantoin. J. Antimicrob. Chemother. 21(1):41-48 Jan. 1988.

34. A Relative Bioavailability (fed) Study of Nitrofurantoin (2 x 50 mg) Capsules. Study #P93-020, May 13, 1993.

35. A Comparative, Randomized, Two-Way, Crossover Bioavailability (fed) Study of Teva Canada and Norwich Eaton (Macrodantin®) 100 mg Nitrofurantoin Macrocrystals Capsules in healthy adult males, Study # 940265, January 4, 1995.

36. Product Monograph for Macrodantin® (nitrofurantoin macro crystals) Capsules, Norwich Eaton Pharmaceuticals, Inc, Date of Preparation: March 28, 1990.

37. FDA-approved label for Macrodantin® (nitrofurantoin macrocrystals) Capsules. Alvogen Inc. USA. Date of Revision: March 2013.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrJAMP NITROFURANTOIN

Nitrofurantoin Macrocrystals Capsules

50 and 100 mg

House Standard

Read this carefully before you start taking Jamp Nitrofurantoin 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 Jamp Nitrofurantoin.

What is Jamp Nitrofurantoin used for?

Jamp Nitrofurantoin is used to treat infections of the urinary tract.

Antibacterial drugs like Jamp Nitrofurantoin treat only bacterial infections. They do not treat viral infections.

How does Jamp Nitrofurantoin work?

Jamp Nitrofurantoin is an antibiotic. It is activated when it is broken down by bacteria. After it is activated, Jamp Nitrofurantoin kills bacteria and prevents the growth of infections.

What are the ingredients in Jamp Nitrofurantoin?

Medicinal ingredients:

nitrofurantoin

Non-medicinal ingredients:

50 mg Capsules: Lactose Monohydrate, Maize Starch, talc. The capsule shell contains Quinoline Yellow, gelatin, titanium dioxide. Printing Material composition: Shellac, Propylene Glycol, Black Iron Oxide and Potassium Hydroxide.

100 mg Capsules: Lactose Monohydrate, Maize starch, talc. The capsule shell contains Quinoline Yellow, gelatin, titanium dioxide. Printing Material composition: Shellac, Propylene Glycol, Black Iron Oxide and Potassium Hydroxide.

Jamp Nitrofurantoin comes in the following dosage forms:

Jamp Nitrofurantoin is available as 50 mg and 100 mg capsule.

Do not use Jamp Nitrofurantoin if:

- you are allergic to any ingredient in Jamp Nitrofurantoin. Make sure to read "What are the ingredients in Jamp Nitrofurantoin?" 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 Jamp Nitrofurantoin 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 Jamp Nitrofurantoin. 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 Jamp Nitrofurantoin 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 Jamp Nitrofurantoin 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 Jamp Nitrofurantoin, 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 Jamp Nitrofurantoin:

Medicines:

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

You should not take Jamp Nitrofurantoin along with medicines that affect your kidneys

Laboratory tests:

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

How to take Jamp Nitrofurantoin:

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

Usual dose:

Adults:	50-100 mg four times a day.
Children:	Dosage should be calculated on the basis of 5-7 mg/kg of body weight per 24 hours given in divided doses four times a day (contraindicated in infants under one month).

If you have a urinary tract infection, your doctor will decide how long you should take Jamp Nitrofurantoin.

Overdose:

If you think you have taken too much Jamp Nitrofurantoin, 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 Jamp Nitrofurantoin, 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 Jamp Nitrofurantoin?

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

Common side effects in people who take Jamp Nitrofurantoin 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 between 15° - 30°C.

Keep out of reach and sight of children.

If you want more information about Jamp Nitrofurantoin:

- 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); or by calling 1-866-399-9091.

This leaflet was prepared by JAMP Pharma Corporation.

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