PRODUCT MONOGRAPH

MACRODANTIN®
(Nitrofurantoin)

50mg, 100mg Capsules

Urinary Tract Antibacterial

Procter & Gamble Pharmaceuticals Canada Inc
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Date of Preparation
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NAME OF DRUG

MACRODANTIN ®

(nitrofurantoin macrocrystals)
capsules, USP

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.

MACRODANTIN is a larger crystal form of nitrofurantoin. The absorption of MACRODANTIN is slower and its urinary excretion 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 are able to take MACRODANTIN capsules without nausea.

INDICATIONS AND CLINICAL USE

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

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

Nitrofurantoin is not indicated for therapy of any systemic infections or for use in prostatitis.

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 infant 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).

MACRODANTIN 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 tumour, and granulosa cell tumour 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.

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.

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 µg/mL all were malformed. None of those exposed to 60 µg/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

The following 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 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 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, eg., *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.

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.

DOSAGE AND ADMINISTRATION

Adults: 50 - 100 mg four times a day.

Children: Should be calculated on the basis of 5-7 mg/kg of body weight per 24

hours to be given in divided doses four times a day (contraindicated under one month).

MACRODANTIN 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 per 24 hours, given in a single or in two divided doses, may be adequate.

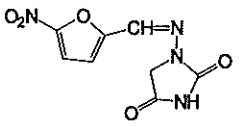
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Nitrofurantoin Macrocrystals

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

Structural Formula:



Molecular Formula: $C_8H_6N_4O$

Molecular Weight: 5238.16

Description

MACRODANTIN (nitrofurantoin macrocrystals) is a synthetic chemical of controlled crystal size. Nitrofurantoin is a stable, yellow, odourless, crystalline compound; very

slightly soluble in water and alcohol and soluble in dimethylformamide and DMSO. Aqueous solubility of nitrofurantoin is a function of both pH and temperature. Nitrofurantoin melts with decomposition at 270 - 272 °C.

Composition

Each capsule contains the following inactive ingredients: edible black ink, carnauba wax, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD & C Yellow #6 and D&C Yellow #10.

Storage

Avoid excessive heat (over 40°C).

AVAILABILITY

MACRODANTIN is available in 50 mg and 100 mg capsules for oral administration.

100 mg: opaque, yellow capsules coded with 3 black bars and Macrodantin, 100 mg, 0149, 0009, bottles of 100's and 500's.

50 mg: opaque, yellow and white capsules coded with 2 black bars and Macrodantin, 50 mg, 0149, 0008, bottles of 100's and 500's.

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
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 MACRODANTIN with food the Cmax, tmax, and elimination $t_{1/2}$ were respectively 100 µg/mL, 3.6 hrs and, 1.13 hrs in urine. Plasma levels do not normally exceed 1 µg/mL following therapeutic administration of MACRODANTIN 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

MACRODANTIN 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 Cmax of 0.05 µg/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 µg/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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