PRODUCT MONOGRAPH

[Pr]TEVA-NITROFURANTOIN

(Nitrofurantoin Macrocrystals)

50 and 100 mg Capsules

USP

Urinary Tract Antibacterial

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Date of Preparation:
May 2, 2018

Submission Control#: 149914

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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.

TEVA-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.

A two-way, blinded, single-dose, crossover bioavailability study was performed on two 50 mg Nitrofurantoin Macrocrystals Capsules, TEVA-NITROFURANTOIN 50 mg capsules and MACRODANTIN® 50 mg capsules, in 24 healthy male volunteers under fed conditions.

The resulting pharmacokinetic parameters are summarized below:

Geometric Mean Arithmetic Mean (C.V.)			
	Teva-Nitrofurantoin (2 x 50mg)	**Macrodantin®** (2 x 50mg)**	**% Ratio of Geometric Means**
Ae_{0-24}[a] (mg)	30.0 30.7 (21)	26.6 27.0 (18)	113
R_{max}[b] (mg/h)	5.70 5.81 (21)	5.05 5.24 (25)	114
T_{Rmax}[C*] (h)	4.46 (1.52)	5.44 (1.50)	-

[a] Ae_{0-24} represents the cumulative excretion over 24 hours.

[b] R_{max} represents the maximum rate of excretion.

[C] T_{Rmax} represents the time of maximum rate of excretion.

* For T_{Rmax} these are the arithmetic means (standard deviation).

** Macrodantin® 50 mg Capsules manufactured by Norwich Eaton Canada Inc., A Procter & Gamble Company, Cambridge, Ontario, Canada.

A two-way, blinded, single-dose, crossover bioavailability study was performed on two 100 mg Nitrofurantoin Macrocrystals Capsules, TEVA-NITROFURANTOIN 100 mg capsules and MACRODANTIN® 100 mg capsules, in 24 healthy male volunteers under fed conditions. The resulting pharmacokinetic parameters are summarized below:

Geometric Mean Arithmetic Mean (C.V.)			
	Teva-Nitrofurantoin (2 x 100mg)	**Macrodantin®** (2 x 100mg)**	**% Ratio of Geometric Means**
Ae_{0-24}[a] (mg)	36.7 37.3 (15)	34.2 34.9 (17)	107
R_{max}[b] (mg/h)	6.77 7.00 (27)	5.60 5.79 (26)	121
T_{Rmax}[C*] (h)	5.25 (1.20)	5.27 (1.90)	-

[a] Ae_{0-24} represents the cumulative excretion over 24 hours.

[b] R_{max} represents the maximum rate of excretion.

[C] T_{Rmax} represents the time of maximum rate of excretion.

* For T_{Rmax} these are the arithmetic means (standard deviation).

** Macrodantin® 100 mg Capsules manufactured by Norwich Eaton Canada Inc., A Procter & Gamble Company, Cambridge, Ontario, Canada.

INDICATIONS AND CLINICAL USE

TEVA-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.

CONTRAINDICATIONS

TEVA-NITROFURANTOIN is contraindicated in the presence of anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine). Treatment in these patients carries an increased risk of toxicity due to impaired excretion of the drug. For the same reason, the drug is much less effective under these circumstances.

Nitrofurantoin 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).

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 s.c. tissue. In one study involving three s.c. 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 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 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).

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenesis 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. TEVA-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.

Impairment of Fertility:

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.

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 s.c. 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 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:

TEVA-NITROFURANTOIN should not be given to women during labor and delivery, or when the onset of labor is imminent (See CONTRAINDICATIONS).

Lactation:

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.

Children:

TEVA-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 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 reactions, fever and eosinophilia occur less 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.

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:

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

Allergic Reactions:

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

Hematologic:

Glucose-6-phosphate dehydrogenase deficiency anemia (see WARNINGS), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia, and eosinophilia have occurred. Inmost 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 because suppression of normal bacterial flora does not occur elsewhere in the body.

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. Nitrofurantoin is dialyzable.

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).

TEVA-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.

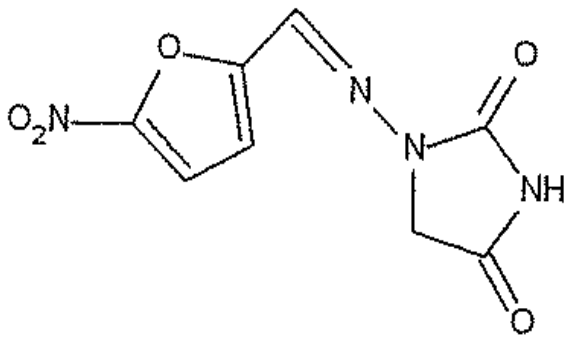
PHARMACEUTICAL INFORMATION

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

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

STABILITY AND STORAGE RECOMMENDATION:

Store between 15° - 30°C, protect from light.

Composition:

50 mg Capsules: Dibasic calcium phosphate dihydrate, pregelatinized starch, talc. The capsule shell contains D&C yellow #10, FD&C yellow #6, gelatin, titanium dioxide.

100 mg Capsules: Lactose, com starch, talc, colloidal silicon dioxide. The capsule shell contains D&C yellow #10, FD&C yellow #6, gelatin, titanium dioxide.

AVAILABILITY OF DOSAGE FORMS

TEVA-NITROFURANTOIN is available as:

50mg- Yellowish white powder in yellow opaque cap and white opaque body, hard gelatin capsules. Printed in black **N** and **50** on opposing cap and body portions of the capsule. **0197**

100 mg- Yellowish white powder in yellow opaque cap and yellow opaque body, size #2 hard gelatin capsules. Printed in black **N** and **100** on the opposing body and cap portions of the capsule.

Supplied in bottles of 100, 500 and 1000 capsules.

MICROBIOLOGY

TEVA-NITROFURANTOIN is bactericidal in urine at therapeutic doses. Its mode of action includes inhibition of bacterial protein synthesis, RNA/DNA synthesis, and energy metabolism. Clinically, bacteria develop only a limited resistance to furan derivatives.

Nitrofurantoin macrocrystals are usually active *in vitro* against the following organisms:

Escherichia coli, enterococci (e.g., *Streptococcus faecalis), Staphylococcus aureus.*

NOTE: Some strains of *Enterobacter* species and *Klebsiella* species are resistant to nitrofurantoin macrocrystals. It is not active against most strains of *Proteus* species, and *Serratia* species. It has no activity against *Pseudomonas* species.

PHARMACOLOGY

TEVA-NITROFURANTOIN is highly soluble in urine, in which it may cause a brown discolouration. Following a therapeutic dose regimen of nitrofurantoin macrocrystal capsules 100 mg qid for 7 days, average urinary drug recoveries (0-24 hours) on day 1 and day 7 were 37.9% and 35.0%, respectively.

Nitrofurantoin is rapidly and completely absorbed from the gastrointestinal tract. Unlike many drugs, the presence of food or agents which delay gastric emptying can increase the bioavailability of nitrofurantoin macro crystals, presumably by allowing better dissolution in gastric juices. The macrocrystalline form of the drug is absorbed and excreted more slowly than microcrystalline nitrofurantoin.

Blood levels of nitrofurantoin remain low and therapeutic concentrations are achieved only in the urine. Following ingestion of recommended doses, antibacterial concentrations are not achieved in plasma because the drug is rapidly eliminated. The plasma half-life is 0.3 to 1 hour. Approximately 40% is excreted unchanged in the urine.

TOXICOLOGY

The relative safety and toxicity profile of nitrofurantoin itself has been established through long clinical use.

In dogs, anhydrous crystals of nitrofurantoin in the larger mesh sizes are significantly less emetic than standard production run nitrofurantoin tablets.

Carcinogenesis:

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 s.c. tissue. In one study involving three s.c. injections of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas were observed in the FI generation.

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Mutagenesis:

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 possible 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 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.

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