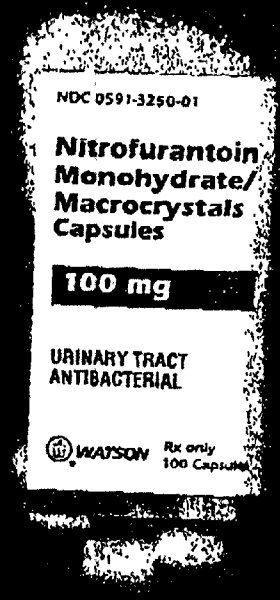
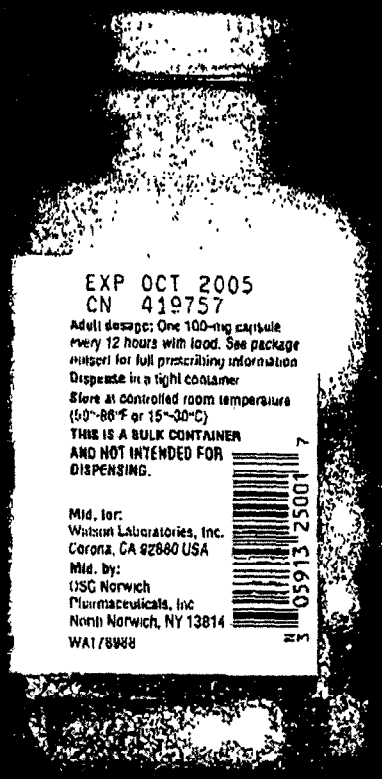
EXHIBIT E


NDC 0591-3250-01
Nitrofurantoin Monohydrate/ Macrocrystals Capsules
100 mg
URINARY TRACT ANTIBACTERIAL
WATSON
Rx only
100 Capsules

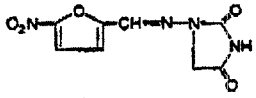

EXP OCT 2005
CN 419757
Adult dosage: One 100-mg capsule every 12 hours with food. See package insert for full prescribing information
Dispense in a tight container
Store at controlled room temperature (59°-86°F or 15°-30°C)
THIS IS A BULK CONTAINER AND NOT INTENDED FOR DISPENSING.
Mfd. for:
Watson Laboratories, Inc.
Corona, CA 92880 USA
Mfd. by:
DSC Norwich
Pharmaceuticals, Inc
North Norwich, NY 13814
WA1/8988
05913 25001 7

Nitrofurantoin Monohydrate/Macrocrystals Capsules

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nitrofurantoin monohydrate/macrocrystals and other antibacterial drugs, nitrofurantoin monohydrate/macrocrystals should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

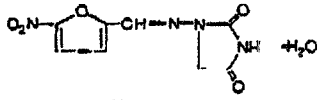
DESCRIPTION: Nitrofurantoin is an antibacterial agent specific for urinary tract infections. Nitrofurantoin Monohydrate/Macrocrystals Capsules are hard gelatin capsule shells containing the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate.

The chemical name of nitrofurantoin macrocrystals is 1-[[[5-nitro-2-furanyl]methylene]amino]-2,4-imidazolidinedione. The chemical structure is the following:



Molecular Weight: 238.16

The chemical name of nitrofurantoin monohydrate is 1-[[[5-nitro-2-furanyl]methylene]amino]-2,4-imidazolidinedione monohydrate. The chemical structure is the following:



Molecular Weight: 256.17

Inactive Ingredients: Each capsule contains carbomer 934P, corn starch, compressible sugar, D&C Yellow No. 10, edible gray ink, FD&C Blue No. 1, FD&C Red No. 40, gelatin, lactose, magnesium stearate, povidone, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY: Each nitrofurantoin monohydrate/macrocrystals 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 powder blend which, upon exposure to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time. Based on urinary pharmacokinetic data the extent and rate of urinary excretion of nitrofurantoin from the 100 mg nitrofurantoin monohydrate/macrocrystals capsule are similar to those of the 50 mg or 100 mg nitrofurantoin macrocrystals capsule. Approximately 20-25% of a single dose of nitrofurantoin is recovered from the urine unchanged over 24 hours.

Plasma nitrofurantoin concentrations after a single oral dose of the 100 mg nitrofurantoin monohydrate/macrocrystals capsule are low, with peak levels usually less than 1 mcg/mL. Nitrofurantoin is highly soluble in urine, to which it may impart a brown color. When nitrofurantoin monohydrate/macrocrystals is administered with food, the bioavailability of nitrofurantoin is increased by approximately 40%.

Microbiology: Nitrofurantoin is bactericidal in urine at therapeutic doses. The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. 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. 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.

Nitrofurantoin, in the form of nitrofurantoin monohydrate/macrocrystals, has been shown to be active against most strains of the following bacteria both *in vitro* and in clinical infections (see **INDICATIONS AND**

n-Positive Aerobes
Staphylococcus saprophyticus

Gram-Negative Aerobes
Escherichia coli

Nitrofurantoin also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance of these data with respect to treatment with nitrofurantoin monohydrate/macrocrystals is unknown:

Gram-Positive Aerobes
Coagulase-negative staphylococci
(including *Staphylococcus epidermidis*)
Enterococcus faecalis
Staphylococcus aureus
Streptococcus agalactiae
Group D streptococci
Viridans group streptococci

Gram-Negative Aerobes
Citrobacter amalonaticus
Citrobacter diversus
Citrobacter freundii
Klebsiella oxytoca
Klebsiella ozaenae

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

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

Susceptibility Tests:
Dilution techniques:
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 32	Susceptible (S)
64	Intermediate (I)
≥ 128	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard nitrofurantoin powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
E. coli ATCC 25922	4-16
S. aureus ATCC 29213	8-32
E. faecalis ATCC 29212	4-16

Diffusion techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 300 µg nitrofurantoin to test the susceptibility of microorganisms to nitrofurantoin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 300-µg nitrofurantoin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
15-16	Intermediate (I)
≤ 14	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for nitrofurantoin.

As with standardized dilution techniques, diffusion

niques. Interpretation involves correlation of obtained in the disk test with the MIC for nitrofurantoin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 300 µg nitrofurantoin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	20-25
S. aureus ATCC 25923	18-22

INDICATIONS AND USAGE: Nitrofurantoin Monohydrate/Macrocrystals Capsules are indicated only for the treatment of acute uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of *Escherichia coli* or *Staphylococcus saprophyticus*.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nitrofurantoin monohydrate/macrocrystals and other antibacterial drugs, nitrofurantoin monohydrate/macrocrystals should be used only to treat or prevent 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 nitrofurantoin monohydrate/macrocrystals are predisposed to persistence or reappearance of bacteriuria (see CLINICAL STUDIES). Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with nitrofurantoin monohydrate/macrocrystals, other therapeutic agents with broader tissue distribution should be selected. In considering the use of nitrofurantoin monohydrate/macrocrystals, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

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

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

Nitrofurantoin Monohydrate/Macrocrystals Capsules are 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. IF THESE REACTIONS OCCUR, NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. REPORTS HAVE CITED PULMONARY REACTIONS AS A CONTRIBUTING CAUSE OF DEATH.

CHRONIC PULMONARY REACTIONS (DIFFUSE INTERSTITIAL PNEUMONITIS, OR PULMONARY FIBROSIS, OR BOTH) CAN DEVELOP INSIDIOUSLY. THESE REACTIONS OCCUR RARELY AND GENERALLY IN PATIENTS RECEIVING THERAPY FOR SIX MONTHS OR LONGER. CLOSE MONITORING OF THE PULMONARY CONDITION OF PATIENTS RECEIVING LONG-TERM THERAPY IS WARRANTED AND REQUIRES THAT THE BENEFITS OF THERAPY BE WEIGHED AGAINST POTENTIAL RISKS (SEE RESPIRATORY REACTIONS).

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

Peripheral neuropathy, which may become severe or

...ropathy, which may become severe or ... has occurred. Fatalities have been reported. ... such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function.

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

Cases of hemolytic anemia of the *primaquine-sensitivity* type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing nitrofurantoin monohydrate/macrocrystals; hemolysis ceases when the drug is withdrawn.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including nitrofurantoin and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS: Information for Patients: Patients should be advised to take nitrofurantoin monohydrate/macrocrystals with food (ideally breakfast and dinner) 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.

Patients should be advised not to use antacid preparations containing magnesium trisilicate while

Nitrofurantoin Monohydrate/ Macrocrystals Capsules

taking nitrofurantoin monohydrate/macrocrystals.

Patients should be counseled that antibacterial drugs including nitrofurantoin monohydrate/macrocrystals should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When nitrofurantoin monohydrate/macrocrystals is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by nitrofurantoin monohydrate/macrocrystals or other antibacterial drugs in the future.

General: Prescribing nitrofurantoin monohydrate/macrocrystals in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions: Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of nitrofurantoin onto the surface of magnesium trisilicate.

Uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. The resulting increase in nitrofurantoin serum levels may increase toxicity, and the decreased urinary levels could lessen its efficacy as a urinary tract antibacterial.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks. Two chronic rodent bioassays utilizing male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF, mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female B6C3F, mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there were increased incidences of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the subcutaneous tissue. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 generation.

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations in L5178Y mouse lymphoma cells. Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells but not in human cells in culture. Results of the sex-linked recessive lethal assay in Drosophila were negative after administration of nitrofurantoin by feeding or by injection. Nitrofurantoin did not induce heritable mutation in the rodent models examined.

The significance of the carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug. Doses of 10 mg/kg/day or greater in healthy human males may, in certain

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

Pregnancy:

Teratogenic effects: Pregnancy Category B. Several reproduction studies have been performed in rabbits and rats, at doses up to six times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to nitrofurantoin. In a single published study conducted in mice at 68 times the human dose (based on mg/kg administered to the dam), growth retardation and a low incidence of minor and common malformations were observed. However, at 25 times the human dose, fetal malformations were not observed; the relevance of these findings to humans is uncertain. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic effects: Nitrofurantoin has been shown in one published transplacental carcinogenicity study to induce lung papillary adenomas in the F1 generation mice at doses 19 times the human dose on a mg/kg basis. The relationship of this finding to potential human carcinogenesis is presently unknown. Because of the uncertainty regarding the human implications of these animal data, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: See **CONTRAINDICATIONS**.

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

Pediatric Use: Nitrofurantoin Monohydrate/Macrocrystals Capsules are contraindicated in infants below the age of one month (see **CONTRAINDICATIONS**). Safety and effectiveness in pediatric patients below the age of twelve years have not been established.

Geriatric Use: Clinical studies of nitrofurantoin monohydrate/macrocrystals 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 in elderly patients should be considered when prescribing nitrofurantoin monohydrate/macrocrystals. 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, it may be useful to monitor renal function.

ADVERSE REACTIONS: 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%). Additional clinical adverse events reported as possibly or probably drug-related occurred in less than 1% of patients studied and are listed below within each body system in order of decreasing frequency:

Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, constipation, emesis

Neurologic: Dizziness, drowsiness, amblyopia

Respiratory: Acute pulmonary hypersensitivity reaction (see **WARNINGS**)

Allergic: Pruritus, urticaria

Dermatologic: Alopecia

Miscellaneous: Fever, chills, malaise

The following additional clinical adverse events have been

owing additional clinical adverse events have been with the use of nitrofurantoin:

Gastrointestinal: Sialadenitis, pancreatitis. There have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment (see **WARNINGS**).

Neurologic: Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility of peripheral neuropathy (see **WARNINGS**).

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

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported rarely. Bulging fontanels, as a sign of benign intracranial hypertension in infants, have been reported rarely.

Respiratory:

CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR WITH THE USE OF NITROFURANTOIN.

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 THEIR DEGREE OF RESOLUTION APPEAR TO BE RELATED TO THE DURATION OF THERAPY AFTER THE FIRST CLINICAL SIGNS APPEAR. PULMONARY FUNCTION MAY BE IMPAIRED PERMANENTLY, EVEN AFTER CESSATION OF THERAPY. THE RISK IS GREATER WHEN CHRONIC PULMONARY REACTIONS ARE NOT RECOGNIZED EARLY.

In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months. If the symptoms are not recognized as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation 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 (see **WARNINGS**).

Changes in EKG (e.g., non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions.

Cyanosis has been reported rarely.

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

Allergic: Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; anaphylaxis; arthralgia; myalgia; drug fever; and chills have been reported. Hypersensitivity reactions represent the most frequent spontaneously-reported adverse events in worldwide postmarketing experience with nitrofurantoin formulations.

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

Hematologic: Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous: As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., *Pseudomonas* species or *Candida* species, can occur.

In clinical trials of nitrofurantoin monohydrate/macrocrystals, the most frequent laboratory adverse events (1-5%), without regard to drug relationship, were as follows: eosinophilia, increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus. The following laboratory adverse events also have been reported with the use of nitrofurantoin: glucose-6-phosphate dehydrogenase deficiency anemia (see **WARNINGS**); agranulocytosis,

nts also have been reported with the use of nitrofurantoin: glucose-6-phosphate dehydrogenase deficiency, anemia (see **WARNINGS**); agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

OVERDOSAGE: Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptoms other than vomiting. Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug. Nitrofurantoin is dialyzable.

DOSAGE AND ADMINISTRATION: Nitrofurantoin Monohydrate/Macrocrystals Capsules should be taken with food.

Adults and Pediatric Patients Over 12 Years: One 100 mg capsule every 12 hours for seven days.

HOW SUPPLIED: Nitrofurantoin Monohydrate/Macrocrystals Capsules are available as 100 mg opaque black and yellow capsules imprinted WATSON on one half and 3250 on the other supplied in bottles of 100.

Store at controlled room temperature (59°-86°F or 15°-30°C).

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically — Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests — Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

CLINICAL STUDIES: Controlled clinical trials comparing nitrofurantoin monohydrate/macrocrystals (Macrobid®) 100 mg p.o. q12h and nitrofurantoin macrocrystals (Macrodantin®) 50 mg p.o. q6h in the treatment of acute uncomplicated urinary tract infections demonstrated approximately 75% microbiologic eradication of susceptible pathogens in each treatment group.

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Macrodantin® is a registered trademark of Procter & Gamble Pharmaceuticals.

Mfd. for: Watson Laboratories, Inc.
Corona, CA 92880 USA
Mfd. by: OSG Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

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