Macrodantin®

Macrodantin® (nitrofurantoin monohydrate) is a synthetic, chemical crystalline derivative. It is a stable, yellow, crystalline compound. Macrodantin® is an antibacterial agent for urinary tract infections. It is available in 25 mg, 50 mg, and 100 mg capsules for oral administration.

Active Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc. Minimum dose, and may contain FD&C Yellow No. 6 and D&C Yellow No. 10.

Clinical Pharmacology: Macrodantin® is a larger crystal form of Furadantin® (nitrofurantoin). The absorption of Macrodantin® is slower and its excretion somewhat less when compared to Furadantin®. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine, in which it may impart a brown color.

Following a dose regimen of 100 mg q.d. for 7 days, average urinary drug concentration (0-24 hours) on day 1 and day 7 were 37.9% and 30.8%.

Unlike many drugs, the presence of food or agents delaying gastric emptying can increase the bioavailability of Macrodantin®, presumably by allowing better dissolution in gastric juices.

Microbiology: Nitrofurantoin is bactericidal in urine at therapeutic doses. The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibiotics. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribonucleic proteins and other macromolecules. As a result of such macromutations, the vital biochemical processes of protein synthesis, aerobically 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 resistance to nitrofurantoin. As the necessary multiple and simultaneous mutations of the target enzymes would most likely be lethal to the bacteria. NITROGEN. With the use of nitrofurantoin has not been a significant problem since its introduction in 1963. 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 Macrodantin®, has been shown to be active against most strains of the following bacteria both in vitro and in clinical infections (see INDICATIONS AND USAGE):

Gram Positive Aerobes
Staphylococcus aureus
Enterococcus (e.g., Enterococcus faecalis)

Gram Negative Aerobes
Escherichia coli

Indications: Macrodantin® is indicated for the treatment of urinary tract infections when susceptible strains of Escherichia coli, enterococci, Staphylococcus aureus, and certain susceptible strains of Klebsiella and Enterobacter species.

Nitrofurantoin is not indicated for the treatment of systemic or gonococcal infections.

Susceptibility Tests: Dilution technique: Quantitative methods using standardized micromethods (MBC) should be used to determine the activity of nitrofurantoin against bacteria. The MIC should be determined by a standardized procedure. This procedure is based on a dilution method (in broth or agar) equivalent to those recommended by the National Committee for Clinical Laboratory Standards. The MIC values should be interpreted according to the following criteria:

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<th>MIC (µg/mL)</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>≤ 5</td>
<td>Susceptible</td>
</tr>
<tr>
<td>6–15</td>
<td>Intermediate(1)</td>
</tr>
<tr>
<td>≥ 16</td>
<td>Resistant</td>
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A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound is used in the urine. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the antimicrobial compound is not the agent of choice, further laboratory tests should be performed for identification of the isolate. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound is used in the urine.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to determine the clinical significance of the results. The equivalent of 50 µg nitrofurantoin should be included on the disk test.

Diffusion technique: The following methods require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to nitrofurantoin. The initial standardized procedure 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.

Interpretation should be based on results using dilution methods. Interpretation involves consideration of the diameter of the zone obtained in the disk test with the MIC for nitrofurantoin.

Indications and Usage: Macrodantin® is specifically indicated for the treatment of urinary tract infections when susceptible strains of Escherichia coli, Enterococcus, Staphylococcus aureus, and certain susceptible strains of Klebsiella and Enterobacter species.

Contraindications: Macrodantin® is contraindicated for the treatment of systemic or gonococcal infections.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Macrodantin® and other antibacterial drugs, Macrodantin® should be used only to treat infections that are known or strongly suspected to be caused by bacteria.

Antagonism has been demonstrated in vitro between nitrofurantoin and various antibiotics. The clinical significance of this finding is unknown.

CONTRAINDICATIONS: Anuria, oliguria, or uncontrolled diabetes mellitus.
Macrodantin (nitrofurantoin macrocrystals)

General: Prescribing Macrodantin 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 concurrently 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.

Urinary tract infections, such as prostatic and radiation cystitis, 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 Feuling'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 4.5 years or to female Sprague-Dawley rats for 2.5 years. Two chronic implantation studies utilizing male and female Sprague-Dawley rats and chronic implantation with Swiss mice and in ICR mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female B6C3F1 mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344 rats, there were increased incidences of uncommon kidney tubular cell neoplasms, osteosarcomas of the bones, and neoplasms of the subcutaneous tissue. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, litters of papillary adenomas of the kidney were observed in the 11th 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 revertant mutation in the rodent models examined.

The significance of the carcinogenicity and mutagenicity of nitrofurantoin is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatic arrest; this is reversible on discontinuing the drug. Doses of 19 mg/kg or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatic arrest with a decrease in sperm count.

Pregnancy: Teratogenic effects: Pregnancy Category B. Several reproductive 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 63 times the human dose (based on mg/kg administered to the dam), growth retardation and a low incidence of minor and normal malformations were observed. However, at 20 times the human dose, total 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 10 times the human dose on a mg/kg basis. The relationship of this finding to potential human carcinogenicity 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: Macrodantin is contraindicated in infants below the age of one month (see CONTRAINDICATIONS).
Dermatologic: Exfoliative dermatitis and exyema multiforme (including Stevens-Johnson syndrome) have been reported rarely. Transient alopecia also has been reported.

Allergic: A lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematus eruptions; pruritus; urticaria, 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.

Gastrointestinal: Nausea, anorexia, and anorexia occur most often. Abdominal pain and diarrhea are less common gastrointestinal reactions. These dose-related reactions can be minimized by reduction of dosage. Glibostrinuria and pancreatitis have been reported. 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).

Hematologic: Cytopenias 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.

Laboratory Adverse Events: The following laboratory adverse events have been reported with the use of nitrofurantoin: increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased mean platelet count, eosinophilia, 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.

OVERDOSE: Occasional incidents of acute overdosage of Macrodantin 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. It is dialyzable.

DOSEAGE AND ADMINISTRATION: Macrodantin should be given with food to improve drug absorption and, in some patients, tolerance.

Adults: 50-100 mg four times a day — the lower dosage levels are recommended for uncomplicated urinary tract infections.

Pediatric Patients: 5-7 mg/kg of body weight per 24 hours, divided into 4 doses (conradined under one month of age).

Therapy should be continued for one week or for at least 3 days after sterilization of the urine is attained. Continued infection indicates the need for reevaluation. For long-term suppressive therapy in adults, a reduction of dosage to 50-100 mg of bedtime may be adequate. For long-term suppressive therapy in pediatric patients, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate. SEE WARNINGS SECTION REGARDING RISKS ASSOCIATED WITH LONG-TERM THERAPY.

HOW SUPPLIED: Macrodantin is available as follows:

25 mg opaque, white capsule impregnated with one black line encircling the capsule and coded "MACRODANTIN 25 mg" and "0149-0007**

NDC 0149-0007-05 bottle of 100

50 mg opaque, yellow and white capsules impregnated with two black lines enclosing the capsule and coded "MACRODANTIN 50 mg" and "0149-0006**

NDC 0149-0006-05 bottle of 100

100 mg opaque, yellow capsules impregnated with three black lines enclosing the capsule and coded "MACRODANTIN 100 mg" and "0149-0009**

NDC 0149-0009-05 bottle of 100

NDC 0149-0009-67 bottle of 1000

Capsule design, registered trademark of Proctor & Gamble Pharmaceuticals.

REFERENCES:


Proctor & Gamble Pharmaceuticals

Cincinnati, Oh 45202

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