Macrobid®
(nitrofurantoin monohydrate/macrocrys
tals)

Capsules

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Macrobid and other antibacterial drugs, Macrobid 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. The Macrobid capsules contain a hard gelatin capsule shell containing the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macr
crys
tals and 75 mg of nitrofurantoin monohydrate.

The chemical name of nitrofurantoin macr
crys
tals is 1-[(5-nitro-2-furanyl)methylene]
aminio]-2-imidazolidinedione. The chemical structure is the following:

Molecular Weight: 238.16

The chemical name of nitrofurantoin monohydrate is 1-[(5-nitro-2-furanyl)methylene]aminio]-2-imidazolidinedione monohydrate. The chemical structure is the following:

Molecular Weight: 259.17

Inactive Ingredients: Each capsule contains car

Reply 

Cebochrome P-430, 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, lact, and titanium dioxide.

CLINICAL PHARMACOLOGY: Each Macrobid 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 Macrobid capsule are similar to those of the 50 mg or 100 mg Macrodantin® (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 Macrobid 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 Macrobid is administered with food, the bioavailability of nitrofurantoin is increased by approximately 40%.

MICROBIOLOGY

Nitrofurantoin is a nitrofuran antimicrobial agent with activity against certain Gram-positive and Gram-negative bacteria.

Mechanism of Action

The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or denature bacterial 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. Nitrofurantoin is bactericidal in vitro at therapeutic doses. 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.

Interactions with Other Antibiotics

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

Development of Resistance

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 the resistance is, at most, a very rare phenomenon.

Nitrofurantoin has been shown to be active against most strains of the following bacteria both in vitro and in clinical infections [see Indications and Usage]:

Aerobic and facultative Gram-positive microorganisms:

Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus agalactiae

Group 0 streptococci
Viridans group streptococci
Acid and facultative Gram-negative microorganisms:

Enterobacteriaceae

Phytophthora infestans

Table 2. Acceptable Quality Control Ranges for Nitrofurantoin

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptibility Interpretive Criteria</th>
<th>Minimum Inhibitory Concentrations (µg/mL)</th>
<th>Disk Diffusion (zone diameter in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>S</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>&gt; 128</td>
<td>&gt; 17</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>S</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>&gt; 64</td>
<td>&gt; 17</td>
</tr>
</tbody>
</table>

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 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 in higher than normal amounts. 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.

Quality Control: Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures (3). Standard nitrofurantoin powder should provide the following range of values noted in Table 1.

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 and young infants of less than 1 month of age.

Macrobid is contraindicated in patients with a history of cholestasis jaundice/hepatocellular dysfunction associated with nitrofurantoin.

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

WARTINGS:

Pulmonary reactions:

ACUTE SUBACUTE, OR CHRONIC PULMONARY REACTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH NITROFURANTOIN. IF THESE REACTIONS OCCUR, MACROBID SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. REPORTS HAVE SUGGESTED THAT PULMONARY REACTIONS MAY BE CAUSED BY THE INTRAVENOUS ADMINISTRATION OF THE DRUG OR AN ACTIVATED KNOT OF 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 WEIGHTED AGAINST POTENTIAL RISKS. (SEE RESPIRATORY REACTIONS.)

Hepatotoxicity:

Hepatic reactions, including hepatitis, cholestasis jaundice, chronic active hepatitis, and hepatitis 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.

Neuropathy:

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, 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 biochemical tests that would indicate neuropathy. If neuropathy occurs, the drug should be withdrawn immediately and appropriate measures should be taken.

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

Hemolytic anemia:

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 Macrobid. Hemolysis occurs when the drug is withdrawn.

Clos turret disease-associated diarrhea:

Clos turret disease-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. Hypotonic producing strains of C. difficile are associated with 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 for change in CDAD in routine use.

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.

This label may not be the latest approved by FDA. For current labeling information, please visit https://www.fda.gov/drugsatfda

Reference ID: 3368447
For current labeling information, please visit https://www.fda.gov/drugsatfda

**PRECAUTIONS:** Information for Patients: Patients should be advised to take Macrodantin 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 antidote preparations containing magnesium trisilicate while taking Macrodantin.

Patients should be counseled that antibacterial drugs including Macrodantin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Macrodantin 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 for the entire prescribed length, even if symptoms disappear before then. Doses of 10 mg/kg/day or greater in adults are associated with a decrease in white blood cell or platelet counts, SLE, and skin eruptions; this is reversible on discontinuing the drug.

Geriatric: Use: Clinical studies of Macrodantin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinically significant differences in responses between the elderly and younger patients. Spontaneous reports suggest a higher proportion of pulmonary reactions, i.e., when 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 are normally 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 Macrodantin. 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. Ancillary, 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 Macrodantin, the most frequent clinical adverse events that were reported as possibly or probably drug-related were nausea (6%), headache (6%), abdominal pain (5%), diarrhea (1%), 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, chill, malaise

The following additional clinical adverse events have been reported with the use of nitrofurantoin:

- Gastrointestinal: Sialadenitis, pancreatitis. There have been sporadic reports of severe pancreatitis associated with the use of nitrofurantoin.
- Dermatologic: Morbilliform, toxic epidermal necrolysis, bullous pemphigoid, and psoriasis.
- Hematologic: Neutropenia, eosinophilia, leukopenia, neutropenia, and thrombocytopenia.
- Neurologic: Peripheral neuropathy, which may become severe or irreversible, has occurred.
- Renal: Nephrotic syndrome, asymptomatic proteinuria, and acute renal failure (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).
- Urogenital: Asymptomatic urinary tract infection, metronidazole-resistant bacterial infection, and urinary tract infection.
- Respiratory: Acute, subacute, or chronic pulmonary hypersensitivity reactions may occur with the use of nitrofurantoin.

CHRONIC PULMONARY REACTIONS OCCURRALLY IN PATIENTS WHO HAVE RECEIVED CONTINUOUS TREATMENT FOR SIX MONTHS OR LONGER. MALAISE, DYSPEPSIA ON EXERTION, COUGH, AND ALTERED PULMONARY FUNCTION ARE COMMON MANIFESTATIONS OF CHRONIC PULMONARY REACTIONS. FINDINGS OF DIFFUSE INTERSTITIAL PNEUMONITIS OR FIBROSIS, OR BOTH, ARE REPORTED IN ASSOCIATION WITH CHRONIC PULMONARY REACTIONS. THE SEVERITY OF CHRONIC PULMONARY REACTIONS AND THEIR DEGREE OF RESOLUTION ARE VARYING. PULMONARY 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 sucubate 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 rarely.

Hepatic: Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and cholestasis, occur rarely. (See WARNINGS.)

Allergic: Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioneurotic, maculopapular, erythematous, or eczematous eruptions; anaphylactic reactions; bulging fontanels, as a sign of increased intracranial pressure; 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.)

CONTRAINDICATIONS.

DOSEAGE AND ADMINISTRATION: Macrodantin capsules should be taken with food. Adults and Pediatric Patients: Over 12 Years. One 100 mg capsule every 12 hours for 7 days.

HOW SUPPLIED: Macrodantin is available as 100 mg opaque black and yellow capsules imprinted “(brand) Macrodantin” on one half and “25427-489” on the other. NDG 52427-285-01 bottle of 100

REFERENCES


CLINICAL STUDIES: Controlled clinical trials comparing Macrodantin 100 mg p.o. q12h and Macrobid 50 mg p.o. 0.5 mg p.o. in the treatment of acute uncomplicated urinary tract infections demonstrated approximately 75% microbiologic eradication of susceptible pathogens in each treatment group. Made in USA

Distributed by: Almac Pharma, Inc.
Pine Brook, NJ 07058 USA

Rec 02/2013 PDC05-010

To request medical information or to report SUSPECTED ADVERSE REACTIONS, contact Alvogen Customer Service at 1-866-770-3024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference ID: 3368447