Macrodantin® (nitrofurantoin macrocrystals) Capsules

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 or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION: Macrodantin is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. Macrodantin is an antibacterial agent for specific urinary tract infections. It is available in 25 mg, 55 mg, and 100 mg capsules for oral administration.

Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, 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, to which it may impart a brown color.

Aerobic and facultative Gram-positive microorganisms:
- Citrobacter freundii
- Citrobacter amalonaticus
- Streptococcus agalactiae

Aerobic and facultative Gram-positive microorganisms:
- At least 90 percent of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) of nitrofurantoin. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) (1) or equivalent standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values should be interpreted according to the criteria provided in Table 1.

- Antagonism has been demonstrated if mutations of the target macromolecules would likely be lethal to the bacteria.

- A report of Susceptibility indicates that the pathogen is 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 standardized inoculum concentrations and standardized susceptibility testing media. Therefore, the values given in Table 1 should be compared only to the criteria given in that table. Inhibitory concentrations (I) are expressed in mcg/ml.

- The zone diameters observed in clinical isolates of the following organisms and the minimum inhibitory concentrations are given in Table 1.

- Macrodantin is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. Macrodantin is an antibacterial agent for specific urinary tract infections. It is available in 25 mg, 55 mg, and 100 mg capsules for oral administration.

- Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, 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, to which it may impart a brown color.

- A report of Susceptibility indicates that the pathogen is 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 standardized inoculum concentrations and standardized susceptibility testing media. Therefore, the values given in Table 1 should be compared only to the criteria given in that table. Inhibitory concentrations (I) are expressed in mcg/ml.

- The zone diameters observed in clinical isolates of the following organisms and the minimum inhibitory concentrations are given in Table 1.

- Macrodantin is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. Macrodantin is an antibacterial agent for specific urinary tract infections. It is available in 25 mg, 55 mg, and 100 mg capsules for oral administration.

- Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, 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, to which it may impart a brown color.

- A report of Susceptibility indicates that the pathogen is 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 standardized inoculum concentrations and standardized susceptibility testing media. Therefore, the values given in Table 1 should be compared only to the criteria given in that table. Inhibitory concentrations (I) are expressed in mcg/ml.

- The zone diameters observed in clinical isolates of the following organisms and the minimum inhibitory concentrations are given in Table 1.

- Macrodantin is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. Macrodantin is an antibacterial agent for specific urinary tract infections. It is available in 25 mg, 55 mg, and 100 mg capsules for oral administration.

- Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, 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, to which it may impart a brown color.

- A report of Susceptibility indicates that the pathogen is 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 standardized inoculum concentrations and standardized susceptibility testing media. Therefore, the values given in Table 1 should be compared only to the criteria given in that table. Inhibitory concentrations (I) are expressed in mcg/ml.

- The zone diameters observed in clinical isolates of the following organisms and the minimum inhibitory concentrations are given in Table 1.

- Macrodantin is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. Macrodantin is an antibacterial agent for specific urinary tract infections. It is available in 25 mg, 55 mg, and 100 mg capsules for oral administration.

- Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD&C Yellow No. 6 and D&C Yellow No. 10.
Patients should be counseled that antibacterial drugs including Macrodantin should only be used to treat bacterial infections. They do not treat viral infections, including flu. 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 exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the drug. In females, antibiotic therapy may result in the overgrowth of nonresistant bacteria. If this occurs, patients should contact their physician as soon as possible.

General: Prescribing Macrodantin in the absence of a proven or strongly suspected bacterial infection 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 has presented evidence of carcinogenic activity in female B6C3F1 mice. 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.

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 correction test assay in Chinese hamster cells, in vitro, and in vivo, have not been done 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 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. 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, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS:

Respiratory:

CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR. CHRONIC PULMONARY REACTIONS OCCUR GENERALLY IN PATIENTS WHO HAVE RECEIVED CONTINUOUS TREATMENT FOR SIX MONTHS OR LONGER. MALAISE, DYSPEPSIA ON EXERTION, COUGH, AND ALTERED PULMONARY FUNCTION ARE COMMON MANIFESTATIONS WHICH CAN OCCUR INSIDIOUSLY. RADIOLOGIC AND HISTOLOGIC FINDINGS OF DIFFUSE INTESTINAL PNEUMATOSIS OR FIBROSIS, OR BOTH, ARE ALSO COMMON MANIFESTATIONS OF THE CHRONIC PULMONARY REACTION. FEVER IS RARELY SEEN TO BEA THREAT TO THE PATIENT. 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 responsive to discontinuation of nitrofurantoin therapy is 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, but 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).

Neurologic: Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatailities 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).

Asthma, vertigo, tinnitus, dizziness, headache, and drowsiness 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 fontanelles, as a sign of benign intracranial hypertension in infants, have been reported rarely.

Dermatologic: Exfoliative dermatitis and erythema 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 rarely. In one case, symptoms included fever, arthralgia, adenopathy, myalgia, optic neuritis, leukopenia, glucocorticoid, drug fever; chills, and vasculitis (sometimes associated with pulmonary reactions) have been reported. Hypersensitivity reactions, including angioedema, have been reported rarely. In one case, anaphylactoid (anaphylactic) reactions to hyperosmolar glucose solutions have been reported rarely.

Gastrointestinal: Nausea, emesis, and anorexia occur most often. Abdominal pain and diarrhea are less common gastrointestinal reactions. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment (see WARNINGS).

Hematologic: Cytopenia 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 serum phosphorus, eosinophilia, granulocytosis, leukopenia, thrombocytopenia, and dysglycemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

OVERDOSAGE: Occasional incidents of acute overdose 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 prevent urinary excretion of the drug. It is dialyzable.

DOSAGE AND ADMINISTRATION: Macrodantin should be given to treat drug absorption and, in some patients, tolerance.

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

Pediatric Patients: 5-7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

Therapy should be continued for one week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for reevaluation.

For long-term suppressive therapy in adults, a reduction of dosage to 50-100 mg at 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 imprinted with “MACRODANTIN 25 mg” and “52427-287”.

NDC 52427-286-01 bottle of 100

50 mg opaque, yellow and white capsule imprinted with “MACRODANTIN 50 mg” and “52427-267”.

NDC 52427-287-01 bottle of 100

NDC 52427-288-01 bottle of 100

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP under a child-resistant closure.

REFERENCES

