CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-045

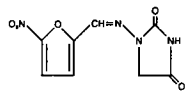
APPROVED LABELING

Labeling: ORIG
NDA No: 16-620 Rec'd. 7-27-88
Reviewed by:

Macrodantin®

(nitrofurantoin macrocrystals)

DESCRIPTION: Macrodantin (nitrofurantoin macrocrystals) 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, 50-mg, and 100-mg capsules for oral administration.



1-[[(5-NITRO-2-FURANYL)METHYLENE]AMINO]-2, 4-IMIDAZOLIDINEDIONE

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. Many patients who cannot tolerate microcrystalline nitrofurantoin are able to take Macrodantin without nausea. It is highly soluble in urine, to which it may impart a brown color.

Following a dose regimen of 100 mg q.i.d. for 7 days, average urinary drug recoveries (0-24 hours) on day 1 and day 7 were 37.9% and 35.0%.

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: Macrodantin, *in vitro*, is bacteriostatic in low concentrations (5-10 mcg/ml) and is considered bactericidal in higher concentrations. Its mode of action is presumed to be interference with several bacterial enzyme systems. Bacteria develop only a limited resistance to furan derivatives.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented: *Escherichia coli*, enterococci (*e.g., Streptococcus faecalis*), *Staphylococcus aureus*, *Staphylococcus epidermidis*.

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

Antagonism has been demonstrated between nitrofurantoin and both nalidixic acid and oxolinic acid *in vitro*.

Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antimicrobial susceptibility. One recommended procedure, (NCCLS, ASM-2)*, uses a disc containing 300 micrograms for testing susceptibility; interpretations correlate zone diameters of this disc test with MIC values for nitrofurantoin. Reports from the laboratory should be interpreted according to the following criteria:

Susceptible organisms produce zones of 17 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15 to 16 mm, indicating that the tested organism would be susceptible if high dosage is used.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

*National Committee for Clinical Laboratory Standards. Approved Standard: ASM-2, Performance Standards for Antimicrobial Disc Susceptibility Tests, July 1975.

[redacted] A bacterial isolate may be considered susceptible if the MIC value for nitrofurantoin is 25 micrograms per ml or less. Organisms are considered resistant if the MIC is 100 micrograms per ml or more.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during drug administration.

INDICATIONS AND USAGE: Macrodantin is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *E. coli*, enterococci, *S. aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses), and certain susceptible strains of *Klebsiella, Enterobacter*, and *Proteus* species.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications. Treatment of this type of patient carries an increased risk of toxicity and is much less effective because of impaired excretion of the drug.

The drug is contraindicated in pregnant patients at term (during labor and delivery) as well as in infants under one month of age because of the possibility of hemolytic anemia in the fetus or in the newborn infant due to immature erythrocyte enzyme systems (glutathione instability).

Macrodantin is 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, MACRODANTIN 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.)

Hepatitis, including chronic active hepatitis, occurs rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients receiving long-term therapy should be monitored periodically for changes in liver function. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures taken.

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy.

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 Negroes and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Macrodantin; hemolysis ceases when the drug is withdrawn.

PRECAUTIONS: Drug Interactions: Magnesium trisilicate, when administered concomitantly with Macrodantin, reduces both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of drug onto the surface of magnesium trisilicate.

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

Carcinogenesis, Mutagenesis: Nitrofurantoin, when fed to female Holtzman rats at levels of 0.3% in a commercial diet for up to 44.5 weeks, was not carcinogenic. Nitrofurantoin was not carcinogenic when female Sprague-Dawley rats were fed a commercial diet with nitrofurantoin levels at 0.1% to 0.187% (total cumulative, 9.25 g) for 75 weeks. Further studies of the effects of chronic administration to rodents are in progress.

Results of microbial *in vitro* tests using *Escherichia coli, Salmonella typhimurium*, and *Aspergillus nidulans* suggest that nitrofurantoin is a weak mutagen. Results of a dominant lethal assay in the mouse were negative.

Impairment of Fertility: The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug.

MAY 13

Doses of 10 mg/kg or greater in healthy human males may, in certain unpredictable instances, produce slight to moderate spermatogenic arrest with a decrease in sperm count.

Pregnancy: The safety of Macrodantin during pregnancy and lactation has not been established. Use of this drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

Labor and Delivery: See CONTRAINDICATIONS.

Nursing Mothers: Nitrofurantoin has been detected in breast milk, in trace amounts. Caution should be exercised when Macrodantin is administered to a nursing woman, especially if the infant is known or suspected to have a glucose-6-phosphate dehydrogenase deficiency.

Pediatric Use: Contraindicated in infants under one month of age. (See CONTRAINDICATIONS.)

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, 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.)

Gastrointestinal: Hepatitis, including chronic active hepatitis, and cholestatic jaundice occur rarely.

Nausea, emesis, 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.

Neurologic: Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility of peripheral neuropathy.

Less frequent reactions, of unknown causal relationship, are nystagmus, vertigo, dizziness, asthenia, headache, and drowsiness.

Dermatologic: Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome) have been reported rarely. Transient alopecia also 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, sialadenitis, pancreatitis, arthralgia, myalgia, drug fever, and chills or chills and fever have been reported.

Hematologic: Agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, glucose-6-phosphate dehydrogenase deficiency anemia, megaloblastic anemia, and eosinophilia have occurred. Cessation of therapy has returned the blood picture to normal. Aplastic anemia has been reported rarely.

Miscellaneous: As with other antimicrobial agents, superinfections by resistant organisms, *e.g., Pseudomonas*, may occur. However, these are limited to the genitourinary tract because suppression of normal bacterial flora does not occur elsewhere in the body.

Macrodantin (nitrofurantoin macrocrystals)

OVERDOSAGE: Occasional incidents of acute overdosage of Macrodantin have not resulted in any specific symptoms other than vomiting. In case vomiting does not occur soon after an excessive dose, 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.

DOSAGE 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 level is recommended for uncomplicated urinary tract infections.

Children: 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 children, 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 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 capsule imprinted with two black lines encircling the capsule and coded "Macrodantin 50 mg" and "0149-0008".*

NDC 0149-0008-05 bottle of 100
NDC 0149-0008-25 MACPAC™, box of 7 DAYCARD™ blisters, 4 capsules each
NDC 0149-0008-66 bottle of 500
NDC 0149-0008-67 bottle of 1000
NDC 0149-0008-77 hospital unit-dose strips in box of 100

100-mg opaque, yellow, capsule imprinted with three black lines encircling the capsule and coded "Macrodantin 100 mg" and "0149-0009".*

NDC 0149-0009-05 bottle of 100
NDC 0149-0009-23 MACPAC™, box of 7 DAYCARD™ blisters, 4 capsules each
NDC 0149-0009-66 bottle of 500
NDC 0149-0009-67 bottle of 1000
NDC 0149-0009-77 hospital unit-dose strips in box of 100

*capsule design, registered trademark of Eaton Laboratories, Inc.

Furadantin/Macrodantin Sensi-Discs for the laboratory determination of bacterial sensitivity are available from BBL, Division of BioQuest. For information on nitrofurantoin assays in blood, serum, and urine, write or call the Medical Department. Literature sent to physicians on request.

Address medical inquiries to Norwich Eaton Pharmaceuticals, Inc., Medical Department, P.O. Box 191, Norwich, NY 13815-0191.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Eaton Laboratories, Inc.
Manati, Puerto Rico 00701

Distributed by
Norwich Eaton Pharmaceuticals, Inc.
A Procter & Gamble Company
Norwich, New York 13815

PRINTED IN U.S.A.

REVISED MAY 1988