NITROFURANTOIN (Systemic)

Category

Antibacterial (systemic).

Indications

Accepted

Urinary tract infections, bacterial (treatment)¾Nitrofurantoin is indicated in the treatment of urinary tract infections caused by susceptible strains of Escherichia coli 37 , enterococci 37 , Staphylococcus aureus 37 , Staphylococcus saprophyticus 38 , Klebsiella species 37, 42 , Enterobacter species 37, 42 , and Proteus species 42.

22, 36

Urinary tract infections, bacterial (prophylaxis)¾Nitrofurantoin is used in the prophylaxis or long-term suppression of urinary tract infections. 37, 42

Not all species or strains of a particular organism may be susceptible to nitrofurantoin. Some strains of Enterobacter or Klebsiella species are resistant to nitrofurantoin. 37, 39 Nitrofurantoin is not active against most strains of Proteus or Serratia species. Nitrofurantoin has no activity against Pseudomonas species. 37, 38, 39

Unaccepted

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses. 37, 38, 39

Nitrofurantoin is not indicated for the treatment of any systemic infection or for prostatitis. 43

Mechanism of action/Effect:

Nitrofurantoin, a synthetic, broad-spectrum, weakly acidic antibacterial, is generally bactericidal at therapeutic concentrations. Therapeutic concentrations are achieved only in the urine. The mechanism of antimicrobial action is unique among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates, which inactivate or alter bacterial ribosomal proteins and other macromolecules. 22, 30 These inactivations or alterations of bacterial ribosomal proteins and macromolecules cause the inhibition of vital biochemical processes of aerobic energy metabolism and the syntheses of bacterial deoxyribonucleic acid (DNA), ribonucleic acid (RNA), cell wall, and protein. 37, 42, 43 The fact that nitrofurantoin interferes with a variety of bacterial processes may explain the lack of acquired bacterial resistance to nitrofurantoin. The multiple and simultaneous mutations of the target macromolecules that would be required to achieve resistance would probably be lethal to the bacteria. 37, 42, 43

Precautions to Consider

Cross-sensitivity and/or related problems

Patients hypersensitive to one nitrofuran may be hypersensitive to other nitrofurans also. 22

Carcinogenicity

Nitrofurantoin, given as 0.3% of the diet to female Holtzman rats for up to 44.5 weeks or given as 0.1% to 0.187% of the diet to female Sprague-Dawley rats for 75 weeks, has not been shown to be carcinogenic. 11 No evidence of carcinogenicity was found in 2 chronic rodent bioassays in male and female Sprague-Dawley rats and 2 chronic bioassays in Swiss mice and in BDF 1 mice. Increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary were seen in female B6C3F 1 mice. There was an increased incidence of uncommon kidney tubular cell neoplasms, osteosarcomas, and neoplasms of the subcutaneous tissue in male F344/N rats. Lung papillary adenomas of unknown significance were observed in the F1 generation of pregnant mice given 75 mg per kg of body weight (mg/kg) of nitrofurantoin by subcutaneous injection. 36

Mutagenicity

Nitrofurantoin has induced point mutations in certain strains of Salmonella typhimurium and forward mutations in L5178Y mouse lymphoma cells. It has also 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 oral or parenteral administration of nitrofurantoin. The medication did not induce heritable mutation in the rodent models examined. 36

Pregnancy/Reproduction

Fertility¾Nitrofurantoin, given in high doses in rats, has been shown to cause temporary spermatogenic arrest, which was reversible upon discontinuation of the medication. Nitrofurantoin, in doses of 10 mg/kg per day or greater, may produce slight to moderate spermatogenic arrest, with decreased sperm counts, in human males. 11

Pregnancy¾Nitrofurantoin crosses the placenta. Use is contraindicated in pregnancy at term and during labor and delivery, or when the onset of labor is imminent, because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems in the fetus. 22, 30, 37, 38, 39, 42

Reproduction studies have been performed in rabbits and rats given doses up to 6 times the human dose; these studies have revealed no evidence of impaired fertility or harm to the fetus due to nitrofurantoin. In a single study conducted in mice given 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, fetal malformations were not observed at 25 times the human dose. 36

In one published transplacental carcinogenicity study, nitrofurantoin has been shown to induce lung papillary adenomas in the F1 generation mice at doses 19 times the human dose on a mg/kg per body weight basis. 37, 38, 39

FDA Pregnancy Category B. 36

Breast-feeding

Nitrofurantoin is distributed into breast milk in trace amounts. Hemolytic anemia may occur, especially in glucose-6-phosphate dehydrogenase (G6PD)-deficient infants. 11

Pediatrics

Use of nitrofurantoin is contraindicated in infants up to 1 month of age because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems. 22 The safety and efficacy of the formulation combining the macrocrystalline and monohydrate forms of nitrofurantoin have not been established in children up to 12 years of age. 38

Geriatrics

No information is available on the relationship of age to the effects of nitrofurantoin in geriatric patients. However, elderly patients are more likely to have an age-related decrease in renal function, which may require a decrease in dosage or change in medication. Side effects, such as acute pneumonitis and peripheral neuropathy, may also occur more frequently in elderly patients.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Hemolytics, other (see Appendix II) 22

(concurrent use with nitrofurantoin may increase the potential for toxic side effects)

Hepatotoxic medications, other (see Appendix II) 2, 22

(concurrent use of nitrofurantoin with other hepatotoxic medications may increase the potential for hepatotoxicity)

Magnesium trisilicate 31, 37, 38, 39, 42

(magnesium trisilicate reduces both the rate and extent of absorption of nitrofurantoin, probably by adsorption of nitrofurantoin to its surface)

Nalidixic acid 28

(nitrofurantoin interferes with the therapeutic effects of nalidixic acid)

>> Neurotoxic medications, other (see Appendix II) 2, 22

(concurrent use of nitrofurantoin with other neurotoxic medications may increase the potential for neurotoxicity)

>> Probenecid or

>> Sulfinpyrazone 11, 37, 38, 39, 42

(these medications may inhibit renal tubular secretion of nitrofurantoin, resulting in increased serum concentrations and/or toxicity, prolonged elimination half-life, and reduced urinary concentrations and effectiveness; dosage adjustment of probenecid may be necessary)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Glucose, urine

(nitrofurantoin may produce metabolites in the urine that may give false-positive results with copper sulfate reduction tests, such as Benedict's solution or Fehling's solution; nitrofurantoin does not interfere with the glucose enzymatic test 37, 38, 39)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]), serum 37, 39 , or

Aspartate aminotransferase (AST [SGOT]), serum 37, 39 , or

Phosphorus, serum 37, 43

(values may be increased)

Hemoglobin 37, 42

(may be decreased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Anemia or

Debilitating disease or

Diabetes mellitus or

Electrolyte imbalance or

Vitamin B deficiency

(these conditions may predispose the patient to peripheral neuropathy from nitrofurantoin 37, 42)

>> Glucose-6-phosphate dehydrogenase (G6PD) deficiency

(hemolysis may occur in patients with G6PD deficiency who take nitrofurantoin)

Hypersensitivity to nitrofurans

>> Neuropathy, peripheral

(nitrofurantoin may cause peripheral neuropathy)

>> Pulmonary disease 30

(nitrofurantoin may cause acute, subacute, and chronic pulmonary reactions, including pneumonitis)

>> Renal function impairment 22, 36

(because nitrofurantoin is excreted through the kidneys, it is recommended that nitrofurantoin not be given to patients with a creatinine clearance of less than 60 mL per minute [1.00 mL per second]; nitrofurantoin loses its effectiveness in patients with renal function impairment, and toxic effects are increased)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Hepatic function determinations 4

(may be required periodically during long-term therapy to detect changes in hepatic function; if hepatitis occurs, nitrofurantoin should be discontinued immediately and appropriate measures taken)

>> Pulmonary function determinations 4, 22

(may be required periodically during long-term therapy if pulmonary reactions [e.g., diffuse interstitial pneumonitis, pulmonary fibrosis] occur; if pulmonary reactions occur, nitrofurantoin should be discontinued and appropriate measures taken)

Renal function determinations

(may be required in patients who receive long-term therapy to determine if changes in renal function have occurred 37)

Side/Adverse Effects

Note: Acute pneumonitis is more common in the elderly; symptoms usually occur within the first week of therapy. Acute pulmonary reactions are often manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on radiograph, and eosinophilia. 37, 38, 39 The pneumonitis is often reversible with discontinuation of the drug; corticosteroids may be beneficial in severe cases. Chronic pulmonary reactions, including diffuse interstitial pneumonitis and fibrosis, are insidious in onset and are more likely to occur in patients who have been on nitrofurantoin therapy for at least 6 months. The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of continued nitrofurantoin therapy after the first clinical signs appear. 37 Pulmonary function may be permanently impaired even after the drug has been stopped, especially if pulmonary reactions are not recognized early. 29 In subacute pulmonary reactions, recovery may require several months after termination of nitrofurantoin treatment. If nitrofurantoin therapy is continued, the symptoms may become more severe. 37 Changes in ECG, such as nonspecific ST/T wave changes or bundle branch block, have been associated with pulmonary reactions. 37

Peripheral neuropathy is an ascending sensorimotor neuropathy, which may be progressive if the drug is not discontinued immediately. Peripheral neuropathy occurs more frequently in patients with renal dysfunction and in the elderly; however, it also occurs in patients with normal renal function who have received nitrofurantoin for prolonged periods of time 37.

Demyelination and degeneration of both sensory and motor nerves occur. Nitrofurantoin should be stopped at the first signs of neuritis. 29

Superinfections with Pseudomonas or Candida can sometimes occur during treatment with nitrofurantoin. 37, 38, 39 These superinfections have been limited to the genitourinary tract. 42

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent 22

Hypersensitivity reactions 37, 38 including anaphylaxis (shortness of breath; swelling of face; changes in facial skin color); angioedema (sudden trouble in swallowing or breathing; swelling of face, mouth, hands, or feet; hoarseness); arthralgia (joint pain); chills; drug fever (fever, shortly after onset of therapy); maculopapular, erythematous, or eczematous eruptions (skin rash); myalgia (muscle pain); pruritus (itching); and urticaria (hives); pneumonitis 37 (chest pain; chills; cough; fever; general feeling of discomfort or illness; troubled breathing)
Incidence less frequent 22, 29

Hematologic reactions, specifically granulocytopenia 37 (sore throat and fever); leukopenia 37 (sore throat and fever); megaloblastic anemia 37 (unusual tiredness or weakness); or thrombocytopenia 37 (rarely, unusual bleeding or bruising; black, tarry stools; blood in urine or stools; pinpoint red spots on skin); neurotoxicity 37 (dizziness; drowsiness; headache; unusual tiredness or weakness); peripheral neuropathy 37 (burning, numbness, tingling, or painful sensations; weakness in arms, hands, legs, or feet)

Incidence rare 3, 22, 34

Aplastic anemia 37 (shortness of breath, troubled breathing, wheezing, or tightness in chest; sores, ulcers, or white spots on lips or in mouth; swollen or painful glands; unusual bleeding or bruising); benign intracranial hypertension 37 (loss of appetite; headache; vomiting; visual changes; bulging fontanel in infants); cyanosis 37 (bluish color of skin)¾secondary to methemoglobinemia; hemolytic anemia 37 (pale skin; unusual tiredness or weakness); hepatotoxicity, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis 37 (yellow eyes or skin; darkening of urine; itching; abdominal or stomach pain, continuing; pale stools or black, tarry stools; headache, continuing; general feeling of discomfort or illness; unpleasant breath odor, continuing; vomiting of blood); optic neuritis 37 (blurred vision or loss of vision, with or without eye pain); pancreatitis 37, 37 (severe stomach pain with nausea or vomiting); pseudomembranous colitis 37 (abdominal or stomach cramps or pain, severe; diarrhea, watery and severe, which may also be bloody; fever); psychological disturbances, such as confusion 37; mental depression 37; and psychotic reactions 37 (mood or mental changes); severe skin reactions, including exfoliative dermatitis, erythema multiforme, and Stevens-Johnson syndrome 37 (blistering, peeling, or loosening of skin and mucous membranes; fever; general feeling of discomfort or illness; red, thickened, or scaly skin; red skin lesions, often with a purple center)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent 22

Gastrointestinal disturbances 37 (abdominal or stomach pain or upset; diarrhea; gas; loss of appetite; nausea or vomiting); headache
Those not indicating need for medical attention

Rust-yellow to brown discoloration of urine 37; transient alopecia 37 (loss of hair, temporary)
Those indicating the need for medical attention if they occur after medication is discontinued

Pseudomembranous colitis 37 (abdominal or stomach cramps or pain, severe; diarrhea, watery and severe, which may also be bloody; fever)

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

Recommended treatment consists of the following: 4, 37

To decrease absorption¾Induction of emesis if vomiting has not already occurred.
Specific treatment¾Maintaining a high fluid intake to promote urinary excretion of nitrofurantoin. Nitrofurantoin is removable from the circulation by dialysis. 37

Supportive care¾Patients in whom intentional overdose is known or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Nitrofurantoin (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to nitrofurans
Pregnancy¾Nitrofurantoin is contraindicated at term and during labor and delivery because of the possibility of hemolytic anemia in the fetus
Breast-feeding¾Not recommended since hemolytic anemia may occur in G6PD-deficient infants
Use in children¾Nitrofurantoin is contraindicated in infants up to 1 month of age because of the possibility of hemolytic anemia
Use in the elderly¾Side effects, such as acute pneumonitis and peripheral neuropathy, may occur more frequently in elderly patients
Other medications, especially other hemolytics, other neurotoxic medications, probenecid, or sulfinpyrazone
Other medical problems, especially G6PD deficiency, peripheral neuropathy, pulmonary disease, or renal function impairment
Proper use of this medication

>> Not giving to infants up to 1 month of age

Taking with food or milk

Proper administration technique for oral liquid

Shaking well before each dose

Using a specially marked measuring spoon or other device

May be mixed with water, milk, fruit juices, or infants' formulas

Proper administration technique for extended-release tablets

Swallowing tablet whole; not breaking, crushing, or chewing before swallowing

>> Compliance with full course of therapy

>> Proper dosage
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

Regular visits to physician to check progress if on long-term therapy

Checking with physician if no improvement within a few days

>> Patients with diabetes: False-positive reactions with copper sulfate urine glucose tests may occur

Side/adverse effects

Rust-yellow to brown discoloration of urine may be alarming to patient although medically insignificant

Signs of potential side effects, especially hypersensitivity reactions, including angioedema, maculopapular, erythematous, or eczematous eruptions, pruritus, urticaria, anaphylaxis, arthralgia, myalgia, drug fever, and chills; pneumonitis; hematologic reactions, specifically granulocytopenia, leukopenia, megaloblastic anemia, or thrombocytopenia; neurotoxicity; peripheral neuropathy; aplastic anemia; benign intracranial hypertension; cyanosis; hemolytic anemia, hepatotoxicity, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis; optic neuritis; pancreatitis; pseudomembranous colitis; psychological disturbances, such as confusion, mental depression, and psychotic reactions; severe skin reactions, including exfoliative dermatitis, erythema multiforme, and Stevens-Johnson syndrome

General Dosing Information

Nitrofurantoin should preferably be taken with food or milk 37.

This minimizes gastrointestinal irritation, delays and increases absorption of both the macrocrystalline and microcrystalline forms, increases the peak concentration of the macrocrystalline form, and prolongs the duration of therapeutic concentrations in the urine. 11

Nitrofurantoin therapy should be continued for seven days or for at least three days after the sterility of the urine is obtained. An infection that continues indicates a need for re-evaluation. 37, 39

Patients on long-term suppressive therapy require a reduction in dose.
Patients with impaired renal function (creatinine clearance less than 60 mL per minute [1.00 mL per second]) should not receive nitrofurantoin since increased toxicity due to possible accumulation of toxic metabolites may occur. 37 Also, nitrofurantoin is ineffective in patients whose creatinine clearance is less than 40 mL per minute.
Due to the lack of broad tissue distribution, many patients treated with nitrofurantoin are predisposed to the persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained both before and after completion of treatment with nitrofurantoin; if persistence or reappearance of bacteriuria occurs, other therapeutic agents with broad tissue distribution should be considered. 37

For treatment of adverse effects

For antibiotic-associated pseudomembranous colitis (AAPMC):
Some patients may develop AAPMC, caused by Clostridium difficile toxin, during or following administration of nitrofurantoin. Mild cases may respond to discontinuation of the drug alone. Moderate to severe cases may require fluid, electrolyte, and protein replacement. In cases not responding to the above measures or in more severe cases, treatment with an antibacterial medication effective against AAPMC may be necessary. 37

Oral Dosage Forms

NITROFURANTOIN CAPSULES USP

Usual adult and adolescent dose

Antibacterial¾
Oral, 50 to 100 mg every six hours. 11, 37, 42 Most uncomplicated infections caused by susceptible bacteria are adequately treated with 50 mg three times a day. 32, 33

Urinary tract infections, bacterial (prophylaxis)¾Oral, 50 to 100 mg once a day at bedtime. 11, 37, 39, 42

Usual adult prescribing limits

Up to 600 mg daily; or up to 10 mg per kg of body weight daily.

Usual pediatric dose

Antibacterial¾
Infants up to 1 month of age: Use is contraindicated because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems. 11

Infants and children 1 month of age and older: Oral, 0.75 to 1.75 mg per kg of body weight every six hours. 11, 30 Therapeutic doses up to 10 mg per kg of body weight daily in four evenly divided doses have been used.
Urinary tract infections, bacterial (prophylaxis):
Infants up to 1 month of age¾Use is contraindicated because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems. 11

Infants and children 1 month of age and older¾Oral, 1 mg per kg of body weight once a day at bedtime. 4, 37, 39, 42 Alternatively, the dose may be given in two divided doses. 37, 39, 42

Strength(s) usually available

U.S.¾25 mg (Rx)[Macrodantin 37 (macrocrystalline)] [Generic] (macrocrystalline 44)

50 mg (Rx)[Macrodantin 37 (macrocrystalline)] [Generic] (macrocrystalline and microcrystalline)

100 mg (Rx)[Macrodantin 37 (macrocrystalline)] [Generic] (macrocrystalline and microcrystalline)

Canada¾25 mg (Rx)[Macrodantin 42 (macrocrystalline)]

50 mg (Rx)[Macrodantin 42 (macrocrystalline)] [Novo-Furantoin 41] [Generic]

100 mg (Rx)[Macrodantin 42 (macrocrystalline)] [Novo-Furantoin 41] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Auxiliary labeling:

· Continue medicine for full time of treatment.
· Take with food or milk.
· May discolor urine.

NITROFURANTOIN EXTENDED-RELEASE CAPSULES

Usual adult and adolescent dose

Antibacterial¾
Oral, 100 mg every twelve hours for seven days. 36, 38, 43

Usual pediatric dose

Antibacterial¾
Children up to 12 years of age: Safety and efficacy have not been established. 36, 38, 43

Children 12 years of age and older: See Usual adult dose .

Strength(s) usually available

U.S.¾100 mg (Rx)[Macrobid 38 (macrocrystalline 25 mg) (monohydrate 75 mg)]

Canada¾100 mg (Rx)[Macrobid 43 (macrocrystalline 25 mg) (monohydrate 75 mg)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Auxiliary labeling:

· Continue medicine for full time of treatment.
· Take with food or milk.
· May discolor urine.

NITROFURANTOIN ORAL SUSPENSION USP

Usual adult and adolescent dose

See Nitrofurantoin Capsules USP .

Usual adult prescribing limits

See Nitrofurantoin Capsules USP .

Usual pediatric dose

See Nitrofurantoin Capsules USP .

Strength(s) usually available

U.S.¾25 mg per 5 mL (Rx)[Furadantin 39 (methylparaben) (propylparaben) (saccharin) (sorbitol)]

Canada¾Not commercially available.

Packaging and storage:

Store between 20 and 25 °C (68 and 77 °F). Store in a tight, light-resistant container. Protect from freezing. 39

Incompatibilities:

Nitrofurantoin and its solutions are discolored by alkalis and by exposure to strong light and decompose upon contact with metals other than stainless steel or aluminum.

Auxiliary labeling:

· Shake well.
· Continue medicine for full time of treatment.
· Take with food or milk.
· May discolor urine.

Note: Dispense in amber bottles.
When dispensing, include a calibrated liquid-measuring device.

Additional information:

The oral suspension dosage form is readily miscible with water, milk, fruit juices, or infants' formulas.

NITROFURANTOIN TABLETS USP

Usual adult and adolescent dose

See Nitrofurantoin Capsules USP .

Usual adult prescribing limits

See Nitrofurantoin Capsules USP .

Usual pediatric dose

See Nitrofurantoin Capsules USP .

Strength(s) usually available

U.S.¾50 mg (Rx) [Generic]

100 mg (Rx) [Generic]

Canada¾50 mg (Rx)[Apo-Nitrofurantoin 40]

100 mg (Rx)[Apo-Nitrofurantoin 40]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Incompatibilities:

Nitrofurantoin and its solutions are discolored by alkalis and by exposure to strong light and decompose upon contact with metals other than stainless steel or aluminum.

Auxiliary labeling:

· Continue medicine for full time of treatment.
· Take with food or milk.
· May discolor urine.

Note: Dispense in amber bottles.

References

1 Furadantin (Norwich-Eaton). PDR Physicians' desk reference. 40th ed. Oradell, NJ: Medical Economics Co; 1986. p. 1278.

2 Drug Interaction review, 1985.

3 Manufacturer's comments, Nitrofurantoin (Systemic), 7/18/84.

4 Furadantin (Norwich-Eaton). PDR Physicians' desk reference. 42nd ed. Oradell, NJ: Medical Economics Co; 1988. p. 1482-3.

5 Reference not used.

6 Macrodantin (Norwich). Red book 1989. p. 449.

7 Nitrofurantoin (generic). Red book 1989. p. 508-9.

8 Ro-Antoin (Phys Form Serv). Red book 1989. p. 616.

9 Macrodantin (Norwich). PDR Physicians' desk reference. 43rd ed. Oradell, NJ: Medical Economics Co; 1989. p. 1486-7.

10 Macrodantin (Norwich). Krogh, CME, editor. CPS Compendium of pharmaceuticals and specialties. 23rd ed. Ottawa: Canadian Pharmaceutical Association; 1988. p. 513.

11 Furadantin (Norwich). PDR Physicians' desk reference. 43rd ed. Oradell, NJ: Medical Economics Co; 1989. p. 1485.

12 Novofuran (Novopharm). Krogh, CME, editor. CPS Compendium of pharmaceuticals and specialties. 23rd ed. Ottawa: Canadian Pharmaceutical Association; 1988. p. 631.

13 Furalan (Lannett). Red book 1989. p. 342.

14 Furan (Am Urological). Red book 1989. p. 342.

15 Furanite (Major). Red book 1989. p. 342.

16 Furatoin (Vortech). Red book 1989. p. 342.

17 Furaton (Cenci). Red book 1989. p. 342.

18 Nitrofor (Kenyon). Red book 1989. p. 508.

19 Nitrofuracot (Truxton). Red book 1989. p. 508.

20 Apo-Nitrofurantoin (Apotex). Krogh, CME, editor. CPS Compendium of pharmaceuticals and specialties. 23rd ed. Ottawa: Canadian Pharmaceutical Association; 1988. p. 67.

21 Nephronex (Cortunon). Krogh, CME, editor. CPS Compendium of pharmaceuticals and specialties. 23rd ed. Ottawa: Canadian Pharmaceutical Association; 1988. p. 599.

22 Nitrofurantoin package insert (Barr), Rev 4/88, Rec 11/88.

23 Canada JR, editor. USP dictionary of USAN and international drug names 1998. Rockville, MD: The United States Pharmacopeial Convention, Inc; 1997. p. 514.

24 Reference not used.

25 Reference not used.

26 AMA Drug Evaluation, 6th ed, 1479-80.

27 Goodman and Gilman's the pharmacological basis of therapeutics. 7th ed. New York: Macmillan, 1985. p. 1110-1.

28 NegGram package insert (Winthrop), Rev 7/86, Rec 2/89.

29 Mandell, Douglas, Bennett, editors. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone; 1990. p. 346-7.

30 Panel comment, 7/2/90.

31 Macrodantin (Norwich-Eaton). PDR Physicians' desk reference 44th ed. Oradell, NJ: Medical Economics Co; 1990. p. 1540-1.

32 AMA Drug Evaluations, 7th ed. Chicago: American Medical Association, 1991. pp II, 8: 15.

33 Panel comment, 6/22/90.

34 Gait JE. Hemolytic reactions to nitrofurantoin in patients with glucose-6-phosphate dehydrogenase deficiency: theory and practice. DICP Ann Pharmacother 12/90; 24: 1210-3.

35 D'Arcy PF. Nitrofurantoin. Drug Intell Clin Pharm 7-8/85; 19: 540-7.

36 Macrobid package insert (Procter & Gamble¾US), Rev 1/92, Rec 7/92.

37 Macrodantin package insert (Procter & Gamble¾US), Rev 2/98, Rec 3/99.

38 Macrobid package insert (Procter & Gamble¾US), Rev 2/98, Rec 3/99.

39 Furadantin (Dura). In: PDR Physicians' desk reference. 53rd ed. 1999. Montvale, NJ: Medical Economics Company; 1999. p. 951-2.

40 Apo-Nitrofurantoin (Apotex). In: Gillis MC, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmacists Association; 1998. p. 113.

41 Novo-Furantoin (Novopharm). In: Gillis MC, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmacists Association; 1998. p. 1170.

42 Macrodantin (Proctor and Gamble). In: Gillis MC, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmacists Association; 1998. p. 931-2.

43 Macrobid (Proctor and Gamble). In: Gillis MC, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmacists Association; 1998. p. 930-1.

44 Electronic Orange Book. Available at http://www.fda.gov/cder/ob/default.htm