CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074976

Trade Name : NITROFURAN CAPSULES (MACROCRYSTALS) USP 50MG AND 100MG

Generic Name: Nitrofuran Capsules (Macrocrystals) USP 50mg and 100mg

Sponsor : Mylan Pharmaceuticals, Inc.

Approval Date: July 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074967

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Statistical Review(s)				
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Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074967

APPROVAL LETTER

ANDA 74-967

JUL 9 1997

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Mr. Sisto:

This refers to your abbreviated new drug application dated September 24, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nitrofurantoin Capsules USP (Macrocrystals), 50 and 100 mg.

Reference is also made to your amendments dated April 18 and June 5, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Nitrofurantoin Capsules USP (Macrocrystals), 50 and 100 mg are bioequivalent and, therefore therapeutically equivalent, to the listed drug (Macrodantin® Capsules 50 and 100 mg, respectively, of Procter & Gamble Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

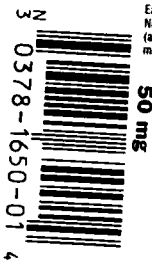
7/9/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074967

FINAL PRINTED LABELING



Each capsule contains Nitrofurantoin, USP (anhydrous macrocrystals) ..... 50 mg

NDC 0378-1650-01

MYLAN®

NITROFURANTOIN CAPSULES, USP (MACROCRYSTALS) 50 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: Adults: 50 to 100 mg q.i.d. with food. See package outsert for indications, precautions and dosage.

Mylan Pharmaceuticals Inc. Morgantown, WV 26505

RM1650A

Each capsule contains Nitrofurantoin, USP (anhydrous macrocrystals) ..... 100 mg

NDC 0378-1700-01

MYLAN

CAPSULES, USP (MACROCRYSTALS)

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

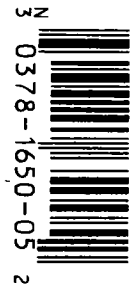
Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: Adults: 50 to 100 mg q.i.d. with food. See package outsert for indications, precautions and dosage.

Mylan Pharmaceuticals Inc. Morgantown, WV 26505

RM1700A



Each capsule contains Nitrofurantoin, USP (anhydrous macrocrystals) ..... 50 mg

NDC 0378-1650-05

MYLAN®

NITROFURANTOIN CAPSULES, USP (MACROCRYSTALS) 50 mg

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: Adults: 50 to 100 mg q.i.d. with food. See package outsert for indications, precautions and dosage.

Mylan Pharmaceuticals Inc. Morgantown, WV 26505

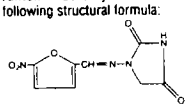
RM1650B

NTFRN:R2

NITROFURANTOIN CAPSULES, USP (MACROCRYSTALS)

50 mg and 100 mg

DESCRIPTION: Nitrofurantoin macrocrystals is a synthetic chemical of controlled crystal size. It is a [redacted] yellow, crystalline compound. Nitrofurantoin macrocrystals is an antibacterial agent for specific urinary tract infections. It is available in 50 mg and 100 mg capsules for oral administration. Nitrofurantoin macrocrystals has the following structural formula:



$C_8H_6N_4O_5$
M. W. 238.16
1-[[(5-nitro-2-furanyl) methylene] amino]-2,4-imidazolidinedione

In addition, each capsule contains the following inactive ingredients: black iron oxide, colloidal silicon dioxide, corn starch, gelatin, lactose monohydrate, magnesium stearate, red iron oxide (50 mg capsule only), silicon dioxide, sodium lauryl sulfate, titanium dioxide, yellow iron oxide, FD&C Blue #2 Aluminum Lake and FD&C Red #40 Aluminum Lake, FD&C Blue #1 Aluminum Lake and D&C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY: Nitrofurantoin macrocrystals is a larger crystal form of nitrofurantoin. The absorption of nitrofurantoin macrocrystals is slower and its excretion somewhat less when compared to nitrofurantoin. Blood concentrations at therapeutic dosage are usually low. 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 nitrofurantoin macrocrystals, 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 antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which [redacted] bacterial ribosomal 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 [redacted]

tic doses. The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal 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. 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. 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 transferable resistance is, at most, a very rare phenomenon.

Nitrofurantoin, in the form of nitrofurantoin macrocrystals, 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
Enterococci
(e.g., Enterococcus faecalis)

Gram-Negative Aerobes:
Escherichia coli

NOTE: Some strains of *Enterobacter* species and *Klebsiella* species are resistant to nitrofurantoin.

Nitrofurantoin also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance of these data with respect to treatment with nitrofurantoin macrocrystals is unknown:

Gram-Positive Aerobes:
Coagulase-negative staphylococci, (including *Staphylococcus epidermidis* and *Staphylococcus saprophyticus)*
Streptococcus agalactiae
Group D streptococci
Viridans group streptococci

Gram-Negative Aerobes:
Citrobacter amalonaticus
Citrobacter diversus
Citrobacter freundii
Klebsiella oxytoca
Klebsiella ozaenae

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

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

Susceptibility Tests: *Diffusion Techniques:* Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard procedure,[1] which has been recommended for use with disks to test susceptibility of organisms to nitrofurantoin, uses the 300-mcg nitrofurantoin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for nitrofurantoin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 300-mcg nitrofurantoin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
>/= 17	Susceptible
15-16	Intermediate
</= 14	Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable urinary levels. A report of "intermediate" indicates that the result be considered equivocal and, if the organism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretations. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

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Standardized procedures require the use of laboratory control organisms. The 300-mcg nitrofurantoin disk should give the following zone diameters:

Organism	Zone Diameter (mm)
E. coli ATCC 25922	20-25
S. aureus ATCC 25923	18-22

Dilution Techniques: Use a standardized dilution method[2] (broth, agar, macrodilution) or equivalent with nitrofurantoin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
</= 32	Susceptible
64	Intermediate
>/=128	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard nitrofurantoin powder should provide the following MIC values:

Organism	MIC (mcg/mL)
E. coli ATCC 25922	4-16
S. aureus ATCC 29213	8-32
E. faecalis ATCC 29212	4-16

INDICATIONS AND USAGE: Nitrofurantoin macrocrystals is specifically indicated for the treatment of urinary tract infections when due to 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 pyelonephritis or perinephric abscesses.

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with nitrofurantoin macrocrystals are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with nitrofurantoin macrocrystals, other therapeutic agents with broader tissue distribution should be selected. In considering the use of nitrofurantoin macrocrystals, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

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 under one month of age.

Nitrofurantoin macrocrystals 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, NITROFURANTOIN

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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 ADVERSE REACTIONS, RESPIRATORY.)

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic 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.

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), anemia, 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 renal function.

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

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 nitrofurantoin macrocrystals; hemolysis ceases when the drug is withdrawn.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including nitrofurantoin, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS: Information For Patients: Patients should be advised to take nitrofurantoin macrocrystals with food to fur-

PRIATE MEASURES [illegible]

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PRECAUTIONS: Information For Patients: Patients should be advised to take nitrofurantoin macrocrystals with food 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.

Many patients who cannot tolerate microcrystalline nitrofurantoin are able to take nitrofurantoin macrocrystals without nausea.

Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking nitrofurantoin macrocrystals.

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_1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female $B6C3F_1$ mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there were increased incidences of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the subcutaneous tissue. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 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 heritable mutation in the rodent models examined.

The significance of the carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug. Doses of 10 mg/kg/day or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatogenic arrest with a decrease in sperm count.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Several reproduction 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 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, at 25 times the human dose, fetal malformations were not observed; the relevance of these findings to humans is uncertain. There are, however, no adequate and well-controlled

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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 19 times the human dose on a mg/kg basis. The relationship of this finding to potential human carcinogenesis 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: Nitrofurantoin macrocrystals is contraindicated in infants below the age of one month. (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.)

Changes in EKG (e.g., nonspecific ST/T wave changes, bundle branch block) have been reported in association with pul-

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., nonspecific 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. Fatalities 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.)

Asthenia, vertigo, and nystagmus 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 fontanels, 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. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; pruritus; urticaria; anaphylaxis; arthralgia; myalgia; drug fever; and chills have been reported.

Gastrointestinal: 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. Sialadenitis 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: Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous: As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., *Pseudomonas* species of *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, 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.

OVERDOSAGE: Occasional incidents of acute overdosage of nitrofurantoin macrocrystals 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.

DOSAGE AND ADMINISTRATION: Nitrofurantoin macrocrystals 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.

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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: Nitrofurantoin Capsules, USP (Macrocrystals) 50 mg and 100 mg are available as follows:

The 50 mg capsules are light brown, opaque capsules imprinted with MYLAN over 1650 in black ink on the cap and body. They are available as follows:

NDC 0378-1650-01
bottles of 100 capsules
NDC 0378-1650-05
bottles of 500 capsules

The 100 mg capsules are grey opaque capsules imprinted with MYLAN over 1700 in black ink on the cap and body. They are available as follows:

NDC 0378-1700-01
bottles of 100 capsules

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Dispense in a tight container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES: 1. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests-Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7. NCCLS, Villanova, PA, 1990.

2. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically-Second Edition. Approved Standard NCCLS Document M7-A2, Vol. 10, No. 8, NCCLS, Villanova, PA, 1990.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED MAY 1997
NTFRN:R2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074967

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
2 (TWO)

2. ANDA NUMBER
74-967

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge
P. O. Box 4310
Morgantown, WV 26504

4. LEGAL BASIS for ANDA SUBMISSION
The applicant has certified that the list drug products referred to in the application are not covered by any patents and exclusivity provisions. The reference listed drug is Macrodantin® manufactured by Procter and Gamble.

5. SUPPLEMENT(s)
None.

6. NAME OF DRUG
None.

7. NONPROPRIETARY NAME
Nitrofurantoin Capsules USP

8. SUPPLEMENT(s) PROVIDE(s) FOR
None.

9. AMENDMENTS AND OTHER DATES

9/24/96	Original application
3/6/97	Minor deficiencies (faxed)
4/18/97	Minor amendment

10. PHARMACOLOGICAL CATEGORY
Antibacterial (urinary)

11. HOW DISPENSED
Prescription (℞)

12. RELATED DMF(s)

13. DOSAGE FORM

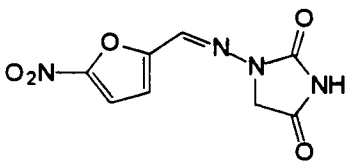
Capsules

14. POTENCY

50 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE

$C_8H_6N_4O_5$. 238.16. 2,4-Imidazolidinedione, 1-[[(5-nitro-2-furanyl)methylene]amino-. 67-20-9. USP 23, page 1085.



16. RECORDS AND REPORTS

None.

17. COMMENTS

None.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER AND DATE COMPLETED

Naiqi Ya, Ph.D./June 23, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074967

BIOEQUIVALENCE REVIEW(S)

ANDA 74-967

JAN 23 1997

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Nitrofurantoin (Macrocrystals) Capsules USP, 50 mg and 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 17 1997

Nitrofurantoin (Macrocrystals)
50, and 100 mg Capsules
ANDA # 74-967
Reviewer: Moheb H. Makary
WP 74967SDW.996

Mylan Pharmaceuticals, Inc.
Morgantown, WV
Submission Date:
September 24, 1996

Review of a Bioequivalence Study, Dissolution Data and Waiver Request

I. Objective:

The firm has submitted a bioequivalence study for its 100 mg Nitrofurantoin (Macrocrystals) Capsules, and dissolution data to compare the test product relative to Procter and Gamble's Macrodantin[R] 100 mg (Macrocrystals) Capsules following a standard meal. The firm has also requested waiver of *in vivo* bioequivalence study requirements for its 50 mg (Macrocrystals) Capsules. To support the request, the firm has submitted comparative dissolution profiles on its Nitrofurantoin (Macrocrystals) 50 mg capsules versus Macrodantin[R] 50 mg (Macrocrystals) Capsules. The test product formulations were also submitted.

II. Introduction:

Nitrofurantoin (macrocrystals) is a synthetic chemical of controlled crystal size. It is an antibacterial agent for specific urinary tract infections.
Following a dose regimen of 100 mg q.i.d. for 7 days, average urinary drug recoveries (0-24 hours) on 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 Nitrofurantoin, presumably by allowing better dissolution in gastric juices.
Nitrofurantoin is available in 25-mg, 50-mg and 100-mg capsules for oral administration.

III. Study Details: (Protocol # 960031, Mylan Project #NITF-9614)

Study site:

Sponsor:	Mylan Pharmaceuticals, Inc. Morgantown, WV
Investigators:	
Study design:	Open-label, randomized, single-dose, two-way, crossover bioavailability study.
Subjects:	However, the protocol specified that 40 volunteers were to be enrolled in the study. Thirty-nine subjects were enrolled in the study after being screened from the general population. Thirty-three subjects completed the study.
Selection criteria:	Healthy male subjects were selected between the ages of 18-45 years with individual weight variation of not more than ± 10% from ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983. Subjects were without a history of benign prostatic hypertrophy, urinary retention, asthma, pulmonary, serious cardiovascular, hepatic, renal, hematopoietic or gastrointestinal disease, alcohol or drug abuse, as evidenced by a medical history and physical examination. Normal glucose-6-phosphate dehydrogenase (G-6-PD) activity, no known allergy to the type of drug being tested. Subjects were free of all medicines and OTC drugs, including aspirin, for at least two weeks before starting the study and during the study. Subjects were also free of any xanthine and caffeine containing products for 48 hours prior to entering the study and until completion of the study.
Dose and treatment:	All subjects completed an overnight fast (10 hours) before any of the following drug treatments: a) Test product: Nitrofurantoin (Macrocrystals) Capsules 1x100 mg (Mylan Pharmaceuticals, Inc.), lot

#2C004C, lot size capsules, manufacturing date 3/96, potency 98.2%, content uniformity 96.9% (%CV=2.0), following a standard breakfast.
b) Reference Product:
Macrodantin^{R} (Macrocrystals) Capsules 1X100 mg (Procter and Gamble), lot # 66039, Exp 10/2000, potency 100.9%, content uniformity 100.2% (%CV=1.9) following a standard breakfast.

Washout period: One week

Food and fluid intake: A standard breakfast was served to all subjects after a supervised overnight fast. Each subject received a standard breakfast consisting of 1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice. An hour later, 1x100 mg (1 capsule) Nitrofurantoin of either test or reference product was administered with 180 mL of water. Lunch was served 5 hours after drug administration. Water was allowed ad lib. except within one hour of drug administration. Standard meals were served during the study. To insure that sufficient urine was produced, subjects were required to drink 240 mL of water one hour before dosing and 180 mL of water at 1, 2, 3, 4, 5, 6, 8, and 10 hours after dosing.

Blood samples: 10 mL blood samples were collected at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 24 hours post-dose. Serial plasma samples were collected, but not analyzed.

Urine samples: Urine samples were collected at predose and at 0-1, 1-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16 and 16-24 hours after dosing. The volume and pH were measured and aliquots were immediately frozen at -80 degree Celsius

for assay.

Subjects welfare: Subjects were housed in the Phoenix facility from 12 hours before until 24 hours after drug administration. Blood pressure and pulse rate were measured before dosing and 24 hours after dosing. Vital signs were taken at other times if deemed necessary.

Assay Methodology:

Statistical Analysis:

The final urinary data were used to calculate the total cumulative amount excreted (TCUMAMT), maximum excretion rate (MAXEXR), time to maximum excretion rate (MAXTEXR), area under the urine excretion rate curve (AUCL) [which is the cumulative amount of urinary excretion, is the sum of the linear trapezoidal estimation of the areas from the time of dosing to the time of the last detectable urinary excretion rate (TLDU)] and the area under the urine excretion rate curve from zero to infinity (AUCI) [AUCI=AUCL+LDU/LEL where LDU is the last detectable urinary excretion rate].
The data were analyzed by analysis of variance (ANOVA). The 90% confidence interval (the two one-sided t-test) was calculated for each of the above pharmacokinetic parameter.

IV. In Vivo Results:

Thirty-nine subjects were enrolled in the study after being screened from the general population. Thirty-three subjects completed the study. Subjects #12, 21, 23, 28 and 37 withdrew from the study prior to period II dosing for personal reasons. Subject #25 was withdrawn from the study due to medical events. In period I, subject #25 experienced feeling of cold, nausea, dizziness, abdominal pain and two events of vomiting. These events began between 12 minutes and 1 day after dosing in period 1 (test product). All events were resolved between 9.7 hours and 1.3 days after period 1 dosing, with the exception of the abdominal pain which was resolved approximately 8 days after period I dosing. The medical director judged the event of feeling cold to be definitely related to something other than the study drug (unknown origin), the nausea as probably related to the study drug, the dizziness as possibly related to the study drug, the abdominal pain to be unlikely related to the study drug and the events of vomiting were judged by the medical director to be probably related to something other than the study drug or study procedures. The total number of adverse events was 17, which consisted of: 8 events that were not related to the study drug and 9 events that were judged to be possibly, probably or unlikely related to the study drug: headache(3), feels dizzy(2), abdominal pain(2), stomach pain(1) and nausea(1).
Urine samples were collected over the scheduled time intervals and urine aliquots were processed as specified in the protocol, with the exceptions indicated in Table I.

Mean urine nitrofurantoin amount excreted and excretion rate are shown below:

Table II

Mean Urinary Nitrofurantoin Excretion Following An Oral Dose Of 100 mg Nitrofurantoin Macrocrystals Capsule

Time hr	Test Mylan Lot #2C004C mg (%CV)	Reference Procter & Gamble Lot#66039 mg (%CV)
-1-0	0	0
0-1	0.16 (217)	0.19 (204)
1-2	1.94 (85.5)	2.05 (84.1)
2-4	8.27 (49.6)	9.61 (46.3)
4-6	11.70 (35.9)	10.30 (33.4)

6-8	8.22 (44.4)	8.34 (44.6)
8-10	3.89 (70.7)	3.32 (66.4)
10-12	1.59 (104)	1.29 (102)
12-14	0.30 (149)	0.31 (170)
14-16	0.21 (255)	0.10 (442)
16-24	0.12 (305)	0.03 (442)

Table III

Nitrofurantoin Urinary Excretion Rate Following An Oral Dose of 100 mg Nitrofurantoin Macrocrystals Capsule Under Fed Conditions

Midpoint Time(hrs)	Test Mylan Lot #2C004C mg/hr (%CV)	Reference Proctor & Gamble Lot #66039 mg/hr (%CV)
0	0	0
0.5	0.16 (217)	0.19 (204)
1.5	1.94 (85.5)	2.05 (84.1)
3	4.13 (49.6)	4.81 (46.3)
5	5.86 (35.9)	5.17 (33.4)
7	4.11 (44.4)	4.17 (44.6)
9	1.95 (70.7)	1.66 (66.4)
11	0.80 (104)	0.65 (102)
13	0.15 (149)	0.16 (170)
15	0.10 (255)	0.05 (186)
20	0.02 (305)	0.00 (442)

	Test	Reference	T/R	90% CI**
TCUMAMT[1] (mg)	36.0(25)	35.5(24)	1.01	96-106%
MAXEXR[2] (mg/hr)	6.54(26)	6.39(28)	1.02	96-110%
MAXTEXR[3](hr)	4.95	4.61		
AUCL[4] (mg)	36.1(25)	34.7(24)	1.04	98-109%
AUCI[5] (mg)	36.4(25)	35.0(24)	1.04	98-109%

** Used Natural Log Transformed Data.

[1] The total cumulative amount of drug excreted over the entire period of sample collection is obtained by adding the amount excreted over each collection time interval.

[2] Maximum excretion rate
[3] Time to maximum excretion rate
[4] Area under the urine excretion rate curve from the time of dosing to the time of the last detectable urine excretion rate.
[5] Area under the urine excretion rate curve from the time of dosing to time to infinity.

1. The total cumulative urinary excretion was 36.0 mg of the Mylan's test product which was 1.4% higher than reference product value. The difference was not statistically significant and the 90% confidence interval was within the acceptable range of 80-125% for the cumulative urinary excretion.

2. The maximum excretion rate and the time to maximum excretion rate of the Mylan's test product were 2.35% and 7.38% higher, respectively, than reference product values. The differences were not statistically significant, and the 90% confidence interval was within the acceptable range of 80-125% for the maximum excretion rate.

3. The AUCL and AUCI of the Mylan's test product were 3.88% and 4.00% higher, respectively, than reference product values. The differences were not statistically significant, and the 90% confidence intervals were within the acceptable range of 80-125% for both parameters.

V. Product Formulation:

Mylan's comparative formulations for its Nitrofurantoin (Macrocrystals) Capsules 50, and 100 mg are shown in Table IV.

VI. In Vitro Dissolution Testing:

Method (USP Method):	USP 23, apparatus I (Basket) at 100 rpm
Medium:	900 mL phosphate buffer pH 7.2
Number of Capsules:	12
Test Products:	Mylan's Nitrofurantoin Macrocrystals Capsules. 50 mg, lot #2C020A 100 mg, lot #2C004C
Reference Products:	Procter & Gamble's Macrodantin 50 mg, lot #64805 100 mg, lot #66039

Dissolution testing results are shown in Table V.

VII. Comments:

1. The in vitro dissolution testing submitted by the firm on it's nitrofurantoin macrocrystals 50 mg and 100 mg capsules is acceptable.

2. Nitrofurantoin Capsules (Macrocrystals), 100 mg and 50 mg, manufactured by Mylan Pharmaceuticals, Inc., exhibited lower dissolution mean values when compared with the reference products at 1, 3 and 8 hours.

3. The formulation for the 50 mg strength is proportionally similar to the 100 mg strength of the test product.

4.The firm's in vivo bioequivalence study under nonfasting conditions is acceptable.

VIII. Recommendations:

1. The bioequivalence study conducted by Mylan Pharmaceuticals, Inc., on its Nitrofurantoin (Macrocrystals), 100 mg Capsule, lot #2C004C, comparing it to Procter & Gamble's Macrodantin^{R}, 100 mg (Macrocrystals) Capsule has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Nitrofurantoin (Macrocrystals), 100 mg Capsule is bioequivalent to the reference product, Macrodantin^{R}, 100 mg Capsule.

2. The dissolution testing conducted by Mylan Pharmaceuticals, Inc., on its Nitrofurantoin (Macrocrystals) 50 mg and 100 mg Capsules, lots #2C020A and 2C004C, respectively, is acceptable. The formulation for the 50 mg strength is proportionally similar to the 100 mg strength of the test product which underwent bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 50 mg (Macrocrystals) Capsules of the test product is granted. The Division of Bioequivalence deems the Nitrofurantoin (Macrocrystals), 50 mg Capsules, manufactured by Mylan Pharmaceuticals, Inc., to be bioequivalent to the Macrodantin^{R}, 50 mg Capsules, manufactured by Procter & Gamble.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test

product should meet the following USP specifications:

1 hour: betweer
3 hour: NLT
8 hour: NLT

4. From the bioequivalence point of view, the firm has met the requirements of the in vivo bioequivalence and in vitro testing and the application is approvable.

The firm should be informed of the above Recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE — 1/14/97

Concur: _____ Date: 1/17/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/1-13-97/WP 74967SDW.996

cc: ANDA # 74-967 original, HFD-658 (Makary), Drug File.

Table V

Drug (Generic Name): Nitrofurantoin (Macrocrystals) Capsules
Dose Strength:100 mg, 50 mg
ANDA No.:74-967
Firm: Mylan Pharmaceuticals, Inc.
Submission Date: September 24, 1996
File Name: 74967SDW.996

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 ml of phosphate buffer pH 7.2
Specifications: 1 hour: between
3 hours: NLT
8 hours: NL
Reference Drug: Macrodantin
Assay Methodology: UV

II. Results of In Vitro Dissolution Testing:

Sampling Times hours	Test Product Lot #2C004C Strength(mg) 100			Reference Product Lot # 66039 Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
1	39		11.0	45		4.4
3	59		15.2	66		8.0
8	73		12.7	86		8.2

Sampling Times hours	Test Product Lot #2C020A Strength(mg) 50			Reference Product Lot # 64805 Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
1	40		7.9	52		9.8
3	61		6.6	81		11.1
8	82		5.8	100		6.8