CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-648

Generic Name:	Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100mg
Sponsor:	Mylan Pharmaceuticals, Inc.
Approval Date:	March 22, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 76-648

MAR 22 2004

Mylan Pharmaceuticals, Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 28, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg.

Reference is also made to your amendment dated August 13, and to your two amendments dated December 12, 2003; and your amendment dated February 12, 2004. We also acknowledge receipt of your correspondence dated May 27, 2003 addressing the patent issues noted below.

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 your Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg, to be bioequivalent and therefore, therapeutically equivalent to the listed drug, Macrobid® Capsules, 100 mg, of Procter and Gamble Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your application, Macrobid® Capsules of Procter and Gamble Pharmaceuticals, Inc., is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 4,772,473 (the '473 patent) and U.S. Patent No. 4,798,725 (the '725 patent), are scheduled to expire on June 16, 2006. Your application contains a paragraph IV patent certification to each patent under section 505(j)(2)(A)(vii)(IV)

of the Act stating that the '473 and '725 patents are invalid, unenforceable, or will not be infringed by your manufacture, use, sale, offer for sale, or importation of Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg under this ANDA. Section 505(j)(5)(B)(iii) of the act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of the '473 or '725 patents which were the subjects of the paragraph IV certifications. This infringement action must be brought against Mylan prior to the expiration of forty-five days from the date the notice Mylan provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for infringement of either the '473 patent or the '725 patent was brought against Mylan Pharmaceuticals, Inc. within the statutory forty-five day period.

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA containing a paragraph IV certification to the '473 and '725 patents. Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity with respect to these patents for Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg. This exclusivity will begin to run from the date Mylan begins commercial marketing of the drug product.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that Mylan will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, 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 and 314.98. 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 final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). 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-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lee Test/for 3/22/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-648

FINAL PRINTED LABELING

NITROFURANTOIN
(Monohydrate/Macrocrystals)
CAPSULES
100 mg
[Twice-a-Day Dosage)

APPROVAL MAR 22 2004

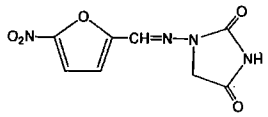
℞ only

ITMM:R1

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nitrofurantoin monohydrate/macrocrystals capsules and other antibacterial drugs, nitrofurantoin monohydrate/macrocrystals capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

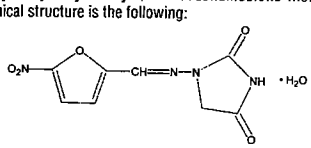
DESCRIPTION: Nitrofurantoin is an antibacterial agent specific for urinary tract infections. Nitrofurantoin monohydrate/macrocrystals has a hard gelatin capsule shell containing the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate.

The chemical name of nitrofurantoin macrocrystals is 1-[[[5-nitro-2-furanyl]methylene]amino]-2,4-imidazolidinedione. The chemical structure is the following:



Molecular Weight: 238.16

The chemical name of nitrofurantoin monohydrate is 1-[[[5-nitro-2-furanyl]methylene]amino]-2,4-imidazolidinedione monohydrate. The chemical structure is the following:



Molecular Weight: 256.17

Each capsule contains the following inactive ingredients: alginic acid, anhydrous dibasic calcium phosphate, black iron oxide, D&C yellow #10 lake, FD&C blue #1 FCF lake, FD&C blue #2 lake, FD&C red #40 AC lake, FD&C yellow #6 lake HT, gelatin, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, red iron oxide, SD-45 alcohol, SDA-3A alcohol, shellac glaze, silicon dioxide, sodium alginate, sodium lauryl sulfate, titanium dioxide and yellow iron oxide.

CLINICAL PHARMACOLOGY: Each nitrofurantoin monohydrate/macrocrystals capsule contains two forms of nitrofurantoin. Twenty-five percent is macrocrystalline nitrofurantoin, which has slower dissolution and absorption than nitrofurantoin monohydrate. The remaining 75% is nitrofurantoin monohydrate contained in a powder blend which, upon exposure to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time. Based on urinary pharmacokinetic data, the extent and rate of urinary excretion of nitrofurantoin from the 100 mg nitrofurantoin monohydrate/macrocrystals capsule are similar to those of the 50 mg or 100 mg nitrofurantoin macrocrystals capsule. Approximately 20 to 25% of a single dose of nitrofurantoin is recovered from the urine unchanged over 24 hours.

Plasma nitrofurantoin concentrations after a single oral dose of the 100 mg nitrofurantoin monohydrate/macrocrystals capsule are low, with peak levels usually less than 1 mcg/mL. Nitrofurantoin is highly soluble in urine, to which it may impart a brown color. When nitrofurantoin monohydrate/macrocrystals is administered with food, the bioavailability of nitrofurantoin is increased by approximately 40%.

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 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 monohydrate/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 saprophyticus

Gram-Negative Aerobes
Escherichia coli

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

Gram-Positive Aerobes
Coagulase-negative staphylococci
(including *Staphylococcus epidermidis*)
Enterococcus faecalis
Staphylococcus aureus
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 antimicrobials. The clinical significance of this finding is unknown.

Susceptibility Tests: ***Dilution Techniques:*** Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation	
≤ 32	Susceptible	(S)
64	Intermediate	(I)
≥ 128	Resistant	(R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard nitrofurantoin powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
E. coli ATCC 25922	4 to 16
S. aureus ATCC 29213	8 to 32
E. faecalis ATCC 29212	4 to 16

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 300 µg nitrofurantoin to test the susceptibility of microorganisms to nitrofurantoin.

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

Zone Diameter (mm)	Interpretation	
≥17	Susceptible	(S)
15 to 16	Intermediate	(I)
≤14	Resistant	(R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for nitrofurantoin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 300 µg nitrofurantoin disk should provide the following zone diameters in these laboratory test quality control strains:

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

INDICATIONS AND USAGE: Nitrofurantoin monohydrate/macrocrystals capsules are indicated only for the treatment of acute uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of *Escherichia coli* or *Staphylococcus saprophyticus.*

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nitrofurantoin monohydrate/macrocrystals capsules and other antibacterial drugs, nitrofurantoin monohydrate/macrocrystals capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with nitrofurantoin monohydrate/macrocrystals capsules are predisposed to persistence or reappearance of bacteriuria. (See CLINICAL STUDIES.) 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 monohydrate/macrocrystals capsules, other therapeutic agents with broader tissue distribution should be selected. In considering the use of nitrofurantoin monohydrate/macrocrystals capsules, 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 to 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 monohydrate/macrocrystals capsules are 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 MONOHYDRATE/MACROCRYSTALS CAPSULES 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.)

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 monohydrate/macrocrystals capsules; 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 monohydrate/macrocrystals capsules with food (ideally breakfast and dinner) to further enhance tolerance and improve drug absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms occur during therapy.

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

Patients should be counseled that antibacterial drugs including nitrofurantoin monohydrate/macrocrystals capsules should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When nitrofurantoin monohydrate/macrocrystals capsule is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by nitrofurantoin monohydrate/macrocrystals capsules or other antibacterial drugs in the future.

General: Prescribing nitrofurantoin monohydrate/macrocrystals capsules in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions: Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of nitrofurantoin onto the surface of magnesium trisilicate.

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

Drug/Laboratory Test Interactions: As a result of the presence of nitrofurantoin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions but not with the glucose enzymatic test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks. Two chronic rodent bioassays utilizing male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF_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 studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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 monohydrate/macrocrystals capsules are contraindicated in infants below the age of one month. (See CONTRAINDICATIONS.) Safety and effectiveness in pediatric patients below the age of twelve years have not been established.

Geriatric Use: Clinical studies of nitrofurantoin monohydrate/macrocrystals capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Spontaneous reports suggest a higher proportion of pulmonary reactions, including fatalities, in elderly patients; these differences appear to be related to the higher proportion of elderly patients receiving long-term nitrofurantoin therapy. As in younger patients, chronic pulmonary reactions generally are observed in patients receiving therapy for six months or longer (see WARNINGS). Spontaneous reports also suggest an increased proportion of severe hepatic reactions, including fatalities, in elderly patients (see WARNINGS).

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing nitrofurantion monohydrate/macrocrystals. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications (see CONTRAINDICATIONS). Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

ADVERSE REACTIONS: In clinical trials of nitrofurantoin monohydrate/macrocrystals, the most frequent clinical adverse events that were reported as possibly or probably drug-related were nausea (8%), headache (6%), and flatulence (1.5%). Additional clinical adverse events reported as possibly or probably drug-related occurred in less than 1% of patients studied and are listed below within each body system in order of decreasing frequency:

Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, constipation, emesis

Neurologic: Dizziness, drowsiness, amblyopia

Respiratory: Acute pulmonary hypersensitivity reaction (see WARNINGS)

Allergic: Pruritus, urticaria

Dermatologic: Alopecia

Miscellaneous: Fever, chills, malaise

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

Gastrointestinal: Sialadenitis, pancreatitis. 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.)

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.

Respiratory: CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR WITH THE USE OF NITROFURANTOIN.

CHRONIC PULMONARY REACTIONS GENERALLY OCCUR 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., non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions.

Cyanosis has been reported rarely.

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

Allergic: Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; anaphylaxis; arthralgia; myalgia; drug fever; and chills have been reported. Hypersensitivity reactions represent the most frequent spontaneously-reported adverse events in worldwide postmarketing experience with nitrofurantoin formulations.

Dermatologic: Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported rarely.

Hematologic: Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous: As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., *Pseudomonas* species or *Candida* species, can occur.

In clinical trials of nitrofurantoin monohydrate/macrocrystals, the most frequent laboratory adverse events (1 to 5%), without regard to drug relationship, were as follows: eosinophilia, increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus. The following laboratory adverse events also have been reported with the use of nitrofurantoin: 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 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. Nitrofurantoin is dialyzable.

DOSAGE AND ADMINISTRATION: Nitrofurantoin monohydrate/macrocrystals capsules should be taken with food.

Adults and Pediatric Patients Over 12 Years: One 100 mg capsule every 12 hours for seven days.

HOW SUPPLIED: Nitrofurantoin monohydrate/macrocrystals capsules are available as 100 mg capsules.

The 100 mg capsules have a light gray opaque cap and a light brown opaque body. The hard-shell gelatin capsule is filled with one orange, round, flat faced tablet with no markings and two yellow, round, flat faced tablets with no markings. The capsule is radially printed with **MYLAN** over **3422** in black ink on both the cap and body. They are available as follows:

NDC 0378-3422-01
bottles of 100 capsules
NDC 0378-3422-05
bottles of 500 capsules

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

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

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically-Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. NCCLS, Villanova, PA, December 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests-Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

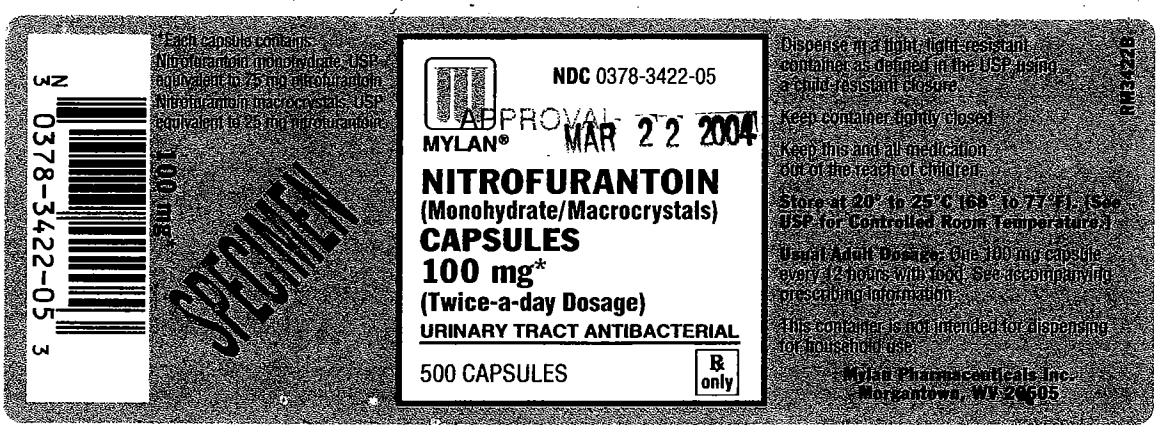
CLINICAL STUDIES: Controlled clinical trials comparing nitrofurantoin monohydrate/macrocrystals 100 mg p.o. q12h and nitrofurantoin macrocrystals 50 mg p.o. q6h in the treatment of acute uncomplicated urinary tract infections demonstrated approximately 75% microbiologic eradication of susceptible pathogens in each treatment group.

MYLAN®

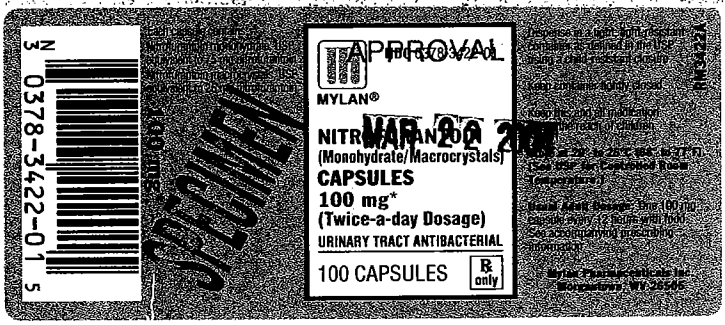
Mylan Pharmaceuticals, Inc.
Morgantown, WV 26505

REVISED AUGUST 2003
NTMM:R1

76-6


Each capsule contains:
Nitrofurantoin monohydrate, USP
equivalent to 25 mg nitrofurantoin
Nitrofurantoin macrocrystals, USP
equivalent to 75 mg nitrofurantoin
100 mg
SPECIMEN
NDC 0378-3422-05
APPROVAL
MAR 22 2004
MYLAN®
NITROFURANTOIN
(Monohydrate/Macrocrystals)
CAPSULES
100 mg*
(Twice-a-day Dosage)
URINARY TRACT ANTIBACTERIAL
500 CAPSULES
Rx only
Dispense in a tight, light-resistant 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 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]
Usual Adult Dosage: One 100 mg capsule every 12 hours with food. See accompanying prescribing information.
This container is not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
0378-3422-05 3
NDA 76-648

76-648


SPECIMEN
APPROVAL
MYLAN®
(Monohydrate/Macrocrystals)
CAPSULES
100 mg*
(Twice-a-day Dosage)
URINARY TRACT ANTIBACTERIAL
100 CAPSULES
Rx only
0378-3422-01 5

76-648

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-648

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-648

Date of Submission: January 28, 2003 (Original Submission)

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg

---

Labeling Deficiencies:

1. CONTAINER (Bottles of 100 and 500)

   a. Revise the established name and strength in the center panel to read:
      NITROFURANTOIN (Monohydrate/Macrocrystals) CAPSULES, 100 mg*
      (Twice-a-day Dosage)

   b. Revise the "Each capsule" statement to read:
      *Each capsule contains:
      Nitrofurantoin monohydrate equivalent to 75 mg nitrofurantoin
      Nitrofurantoin macrocrystals equivalent to 25 mg nitrofurantoin.

2. INSERT

   a. GENERAL: throughout the insert, revise "[redacted]*" to read "nitrofurantoin macrocrystals"
   b. TITLE: Revise the established name and strength to read:
      NITROFURANTOIN (Monohydrate/Macrocrystals) CAPSULES, 100 mg
      (Twice-a-day Dosage)
   c. DESCRIPTION, Inactive ingredients: revise "[redacted]" to read "hypromellose"
   d. WARNINGS
      i. First paragraph, second sentence: "...NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES SHOULD BE..."
      ii. Sixth paragraph (beginning with "Cases of..."), last sentence: "...discontinuing nitrofurantoin monohydrate/macrocrystals capsules; hemolysis..."
   e. PRECAUTIONS, Geriatric Use:
      i. First sentence: "...studies of nitrofurantoin monohydrate/macrocrystals capsules did not..."
      ii. Second sentence: "...clinical experience has not identified..." [delete "[redacted]"
   f. Delete the sentence: "[redacted]"

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

The capsule shell and imprinting ink contain yellow iron oxide, red iron oxide, and black iron oxide. Would taking 2 capsules exceed 5 mg/day of elemental iron (refer to 21 CFR 73.1200 (c))? No. Ring Wilday Cai

FOR THE RECORD: **First Generic**

1. MODEL LABELING - This labeling review was based on the reference listed drug, (Macrobid® Capsules - Proctor and Gamble Pharmaceuticals; NDA 20-064/S-013; revised June 2002; approved February 4, 2003).

   Macrobid consists of 25% macrocrystalline nitrofurantoin and 75% nitrofurantoin monohydrate, while Macrodantin is 100% nitrofurantoin macrocrystals. Mylan's Generic version of Macrodantin (74-967) was approved July 9, 1997.

   Drug Substance is USP
   Packaging and storage— Preserve in tight, light-resistant containers.
   Labeling— Capsules that contain the macrocrystalline form of Nitrofurantoin are so labeled.

   Drug Product is non-USP

2. PATENTS AND EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020064	001	4772473	JUN 16,2006	
020064	001	4798725	JUN 16,2006	

Exclusivity Data-There is no unexpired exclusivity for this product.

Mylan provided a paragraph IV certification for the '473 and '725 patents. [Vol. A1.1, pg. 10-11]

3. MANUFACTURING FACILITY (Vol. A1.9, pg. 4234)
   Mylan Pharmaceuticals Inc.
   781 Chestnut Ridge Road
   Morgantown, WV 26504-4310

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   ANDA - Store at controlled room temperature, between 15°C and 30°C (59° F and 86°F)(see USP)
   USP - Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:
   NDA -Pharmacist: Dispense in a tight, light resistant, child-resistant container
   ANDA - Pharmacist: Dispense in a tight, light resistant container as defined in the USP, with a child-resistant closure (as required).
   USP - Preserve in tight, light-resistant containers.

6. INACTIVE INGREDIENTS:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in Vol. A1.9 on pages:
   Nitrofurantoin monohydrate and macrocrystals formulation: pg. 3954
   Empty capsule body and cap & [redacted] components: Pg. 3955
   Silicon Dioxide [redacted] pg. 3958

7. PRODUCT LINE:
   The innovator markets its product in bottles of 100.
   The applicant proposes to market its product in bottles of 100 and 500.

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.11, pg. 5303)

   100s: 150 cc round beige HDPE; 38 mm, beige, plastic crc
   500s: 24 oz., oblong beige HDPE; 53 mm beige, plastic closure

9. PRODUCT DESCRIPTION:

   The capsule debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The capsules are described as follows:

   "A No. 0, light gray opaque (0945) cap/light brown opaque (3826) body, hard-shell gelatin capsule filled the one orange, 1/4" round, flat faced tablet with no markings and two yellow, 1/4" round flat faced tablets with no markings. The capsule is radially printed with MYLAN over 3422 in black ink on both the cap and the body. "[COA: Vol. 1.10, pg. 4659]

10. BIOEQUIVALENCE: Review pending

Date of Review: April 7, 2003 Date of Submission: January 28, 2003 (Original Submission)

Primary Reviewer: Ruby Wu RWu Date: 6/23/03

Team Leader: John Grace John J Grace Date: 6/23/2003

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cc: ANDA: 76-648
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
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Review

First Generic

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-648
Date of Submission: August 13, 2003 (Amendment-FPL)
Applicant's Name: Mylan Pharmaceuticals Inc.
Established Name: Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg

---

APPROVAL SUMMARY
Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER (Bottles of 100 and 500):
Satisfactory in final print as of the August 13, 2003 submission. [Vol. B2.1, Attachment D]

Professional Package INSERT:
Satisfactory in final print as of the August 13, 2003 submission. [Vol. B2.1, Rev. August 2003]

Revisions needed post-approval: No

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Macrobid®

NDA Number: 20-064

NDA Drug Name: Nitrofurantoin Monohydrate/Macrocrystals Capsules

NDA Firm: Proctor and Gamble Pharmaceuticals

New RLD labeling approved on 10/30/03 (NDA 20-064/S14). S-14 provided for revisions to the insert to comply with "Labeling requirements for systemic ant. bacterial drug products intended for human use." Mylan already had this language in their labeling. Therefore, Mylan's insert remains current. Ruby Wu 3/1/04

Date of Approval of NDA Insert and supplement: NDA 20-064/S-013; revised June 2002; approved February 4, 2003. The TITLE, INDICATIONS AND USAGE, and PRECAUTIONS sections have also been revised to comply with Federal Register Docket No. 00N-1463 "Labeling requirements for systemic antibacterial drug products intended for human use." Note: There is a note to the chemist in Labeling Review #1

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	How Filed	Labeling Impact
020064	001	4772473	JUN 16,2006	IV	None
020064	001	4798725	JUN 16,2006	IV	None

Exclusivity Data: There is no unexpired exclusivity.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD: **First Generic**

see Basis for approval (pg. 1)

1. MODEL LABELING - This labeling review was based on the reference listed drug, (Macrobid® Capsules - Proctor and Gamble Pharmaceuticals; NDA 20-064/S-013; revised June 2002; approved February 4, 2003).

   The TITLE, INDICATIONS AND USAGE, and PRECAUTIONS sections have also been revised to comply with Federal Register Docket No. 00N-1463 "Labeling requirements for systemic antibacterial drug products intended for human use." Final Rule published in Vol. 68, No. 5, Thursday, February 6, 2003.

   Macrobid consists of 25% macrocrystalline nitrofurantoin and 75% nitrofurantoin monohydrate, while Macrodantin is 100% nitrofurantoin macrocrystals. Mylan's Generic version of Macrodantin (74-967) was approved July 9, 1997.

   Drug Substance is USP
   Packaging and storage— Preserve in tight, light-resistant containers.
   Labeling— Capsules that contain the macrocrystalline form of Nitrofurantoin are so labeled.

   Drug Product is non-USP

2. PATENTS AND EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	How Filed	Labeling Impact
020064	001	4772473	JUN 16,2006	IV	None
020064	001	4798725	JUN 16,2006	IV	None

Exclusivity Data-There is no unexpired exclusivity for this product.

Mylan provided a paragraph IV certification for the '473 and '725 patents. [Vol. A1.1, pg. 10-11]

3. MANUFACTURING FACILITY (Vol. A1.9, pg. 4234)
   Mylan Pharmaceuticals Inc.
   781 Chestnut Ridge Road
   Morgantown, WV 26504-4310

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   ANDA -Same as RLD
   USP - Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:
   NDA -Pharmacist: Dispense in a tight, light resistant, child-resistant container
   ANDA - Pharmacist: Dispense in a tight, light resistant container as defined in the USP, with a child-resistant closure (as required).
   USP - Preserve in tight, light-resistant containers.

6. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in Vol. A1.9 on pages:
Nitrofurantoin monohydrate and macrocrystals formulation: pg. 3954
Empty capsule body and cap & [illegible] components: Pg. 3955
Silicon Dioxide [illegible] pg. 3958

7. PRODUCT LINE:
The innovator markets its product in bottles of 100.
The applicant proposes to market its product in bottles of 100 and 500.

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.11, pg. 5303)

100s: 150 cc round beige HDPE; 38 mm, beige, plastic crc
500s: 24 oz., oblong beige HDPE; 53 mm beige, plastic closure

9. PRODUCT DESCRIPTION:

The capsule debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The capsules are described as follows:

"A No. 0, light gray opaque (0945) cap/light brown opaque (3826) body, hard-shell gelatin capsule filled the one orange, 1/4" round, flat faced tablet with no markings and two yellow, 1/4" round flat faced tablets with no markings. The capsule is radially printed with MYLAN over 3422 in black ink on both the cap and the body. "[COA: Vol. 1.10, pg. 4659]

10. BIOEQUIVALENCE: Review pending

Date of Review: August 28, 2003 Date of Submission: August 13, 2003

Primary Reviewer: Ruby Wu RWu Date: 8/25/03

Team Leader: John Grace John J Grace Date: 9/9/2003

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cc: ANDA: 76-648
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-648

CHEMISTRY REVIEW(S)

ANDA 76-648

Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg

Mylan Pharmaceuticals, Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-648

2. REVIEW #: 01

3. REVIEW DATE: April 22, 2003
Revised on: June 23, 2003

4. REVIEWER: Ramnarayan S. Randad

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Mylan:	
Original submission	January 28, 2003
NC	May 27, 2003

FDA:	Document Date
Acknowledgement letter (acceptable for filling: 01/29/03)	03/10/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	January 28, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharamceutical, Inc.
Address:	781 Chestnut Ridge Road, P. O. Box 4310, Morgantown, WV 26504-4310
Representative:	Frank R. Sisto
Telephone:	304-599-2595
FAX:	304-285-6407

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Nitrofurantoin Monohydrate/ Macrocrystals

9. LEGAL BASIS FOR SUBMISSION: 505(J)

Reference Product: Macrobid® (Nitrofurantoin Monohydrate/Macrocrystals). 100 mg Capsule contains 75 mg of Nitrofurantoin Monohydrate & 25 mg of Nitrofurantoin Macrocrystals

Manufacturer: Proctor & Gamble
NDA # 020064

	Patent #	Expiration Date	Use Code
Patent	4,772,473 and 4,798,725	June 16, 2006	
Exclusivity	None		

Page 10: ANDA 76-648 is submitted under paragraph IV. Mylan certifies that US patent # 4,772,473 and 4,798,725 are invalid, unenforceable or will not be infringed by the manufacture, sale, use, offer to sale, or importation of Nitrofurantoin Monohydrate/ Macrocrystals Capsules, 100 mg. Firm certifies that as per "electronic Orange Book" the reference product is not covered by any exclusivity provisions. Firm state that in pursuant of section 505(j)(2)(B)(i) of FDA, Mylan will provide notice to each owner of the patents which are subject of the certification, or to the holder claiming said patents.

Page 19: Mylan certifies that the active ingredient of the proposed DP [Nitrofurantoin Monohydrate/Macrocystals, Capsule] have been previously approved for the RLD Macrobid®. Firm states that the route of the administration, dosage form, and the strength of the proposed DP are same as that of the RLD.

NC May 27, 2003: Mylan states that they have not received any notice regarding paragraph IV litigation. Thus firm states that they will market DP upon approval of this application.

10. PHARMACOL. CATEGORY: Antibacterial; for treatment acute cystitis (urinary track infection caused by E. coli or Staphylococcus saprophyticus)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

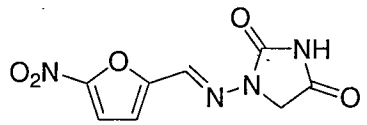
_____SPOTS product - Form Completed

__X__Not a SPOTS product

APPEARS THIS WAY
ON ORIGINAL

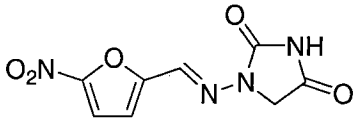
16.CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[(5-nitrofurfurylidene)amino]hydantoin



CAS: *67-20-9*
Molecular Weight: 238.2
Molecular formula: $C_8H_6N_4O_5$

1-[(5-nitrofurfurylidene)amino]hydantoin monohydrate



.H_2O

CAS: *17140-81-7*
Molecular Weight: 256.17
Molecular formula: $C_8H_6N_4O_5$ .H_2O

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (p. 6):

DMF #	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
	II			1	inadequate	4/21/03	Rev #1 by Dr. R. S. Randad
	II			1	inadequate	04/13/03	Rev #2 by Dr. R. S. Randad
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III						
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application

5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Related NDA/ANDA (s):

As of this review date 4/13/03 OGD has not approved ANDA for Nitrofurantoin Monohydrate/Macrocrystals combination DP. However, following ANDA's for Nitrofurantoin have been approved by OGD:

FIRM NAME	ANDA #	STRENGTH	STATUS	DATE
Ivax	73-652	100 mg	Approved	01/28/93
Ivax	73-671	50 mg	Approved	01/28/93
Watson	73-696	25, 50, 100 mg	Approved	12/31/92
Geneva	74-336	25, 50, 100 mg	Approved	01/25/95
Mylan	74-967	50 mg, 100 mg	Approved	07/09/97
Lannett	80-017	Tab	Approved	09/30/70
Eon	80-043	tab	Approved	11/25/70

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	03/24/03	J. D. Ambrogio (HFD 322)
Methods Validation	Not submitted, DS is in USP. Minor issues with DP are pending resolution		
Labeling	Deficient (Sent)	6/23/03	R. Wu
Bioequivalence	pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No
If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-648

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #76-648 is not approvable pending clarification of minor chemistry/Labeling issues. The bio-equivalency information is pending review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance Nitrofurantoin Monohydrate is lemon-yellow powder, and Nitrofurantoin Macrocrystals is Brown-yellow crystalline powder.

- The drug substance exists in two polymorphic forms, anhydrous Macrocrystals and Monohydrate. Firm controls for these forms with specifications NMT and between respectively.

- The drug product, Nitrofurantoin Monohydrate/Macrocrystals (75/25) is available as 100 mg capsules . Each capsule contains twenty-five (25%) percent of Nitrofurantoin Macrocrystals, which has slower dissolution and absorption than Nitrofurantoin Monohydrate and the remaining 75% is Nitrofurantoin Monohydrate.

- The DP formulation is as follows: Nitrofurantoin Monohydrate as extended release, and Nitrofurantoin Macrocrystals as immediate release.

- The capsule have a light gray Opaque cap and light brown Opaque body. Each hard shell gelatin capsule is filled with one

orange Nitrofurantoin Macrocrystals and two yellow round flat face Nitrofurantoin Monohydrate tablets with no markings.

- Nitrofurantoin Monohydrate/Macrocrystals capsules is labeled for an oral use. Mylan's Nitrofurantoin Monohydrate/ Macrocrystals are dispensed in bottles of 100 and 500 capsules. The beige HDPE bottles and closure with [redacted] meet the requirement as well-closed containers.

- The drug substance (DS) is an official article. Firm's analytical methods are based upon current USP and they are satisfactory.

- The drug product (DP) combination (75/25) is not listed in the current USP. Firm has developed validated methods to control ID, related compounds, strength, quality and purity of DP and they are satisfactory. There are some minor issues regarding the DP specifications that need to be resolved.

- The acceptability of the current dissolution specifications are contingent up on the acceptance by the Division of Bioequivalence (DBE).

B. Description of How the Drug Product is Intended to be Used

- The dose for the Nitrofurantoin Monohydrate/Macrocrystal capsules should be individualized. The recommended dose for adults and pediatric patients over 12 years is one 100 mg every 12-hours for seven days. The Nitrofurantoin Monohydrate /Macrocrystals capsule should be taken with food.

- Tablets are to be stored under the CRT 15-30^{0}C (59-86 ^{0}F) and dispensed in a tight, light resistant containers. The expiration dating for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- MINOR Chemistry Issues
- Labeling issues
- Pending Bio-equivalency review

III. Administrative

A. Reviewer's Signature

Ramnarayan S. Randad

B. Endorsement Block

HFD-620/Ramnarayan S. Randad, Ph.D./6/24/03 RSrandad 7/1/03
HFD-620/Shing Liu, Team Leader/6/25/03 SL 7/1/03
HFD-617/Wanda Pamphil, Pharm. D./6/30/03 for 7/2/03

V:\FIRMSAM\MYLAN\LTRS&REV\76648.CR01.NA.DOC

C. CC Block

ANDA 76-648
ANDA DUP
DIV FILE
Field Copy

APPEARS THIS WAY
ON ORIGINAL

Redacted 33

Page(s) of trade secret and /or confidential commercial information

ANDA 76-648

Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg

Mylan Pharmaceuticals, Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-648

2. REVIEW #: 02

3. REVIEW DATE: September 25, 2003
Revised on: October 9, 2003
Revised on: November 10, 2003

4. REVIEWER: Ramnarayan S. Randad

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Mylan:	
Original submission	January 28, 2003
NC	May 27, 2003

FDA:	Document Date
Acknowledgement letter (acceptable for filling: 01/29/03)	03/10/03
Deficiency letter	07/09/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (Labeling)	August 13, 2003
Minor Amendment	September 05, 2003
Telephone Amendment	October 07, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharamceutical, Inc.
Address:	781 Chestnut Ridge Road, P. O. Box 4310, Morgantown, WV 26504-4310
Representative:	Frank R. Sisto
Telephone:	304-599-2595
FAX:	304-285-6407

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Nitrofurantoin Monohydrate/ Macrocrystals

9. **LEGAL BASIS FOR SUBMISSION:** 505(j)

Reference Product: Macrobid® (Nitrofurantoin Monohydrate/Macrocrystals). 100 mg Capsule contains 75 mg of Nitrofurantoin Monohydrate & 25 mg of Nitrofurantoin Macrocrystals
Manufacturer: Proctor & Gamble
NDA # 020064

	Patent #	Expiration Date	Use Code
Patent	4,772,473 and 4,798,725	June 16, 2006	
Exclusivity	None		

Page 10: ANDA 76-648 is submitted under paragraph IV. Mylan certifies that US patent # 4,772,473 and 4,798,725 are invalid, unenforceable or will not be infringed by the manufacture, sale, use, offer to sale, or importation of Nitrofurantoin Monohydrate/ Macrocrystals Capsules, 100 mg. Firm certifies that as per "electronic Orange Book" the reference product is not covered by any exclusivity provisions. Firm state that in pursuant of section 505(j)(2)(B)(i) of FDA, Mylan will provide notice to each owner of the patents which are subject of the certification, or to the holder claiming said patents.

Page 19: Mylan certifies that the active ingredient of the proposed DP [Nitrofurantoin Monohydrate/Macrocystals, Capsule] have been previously approved for the RLD Macrobid®. Firm states that the route of the administration, dosage form, and the strength of the proposed DP are same as that of the RLD.

NC May 27, 2003: Mylan states that they have not received any notice regarding paragraph IV litigation. Thus firm states that they will market DP upon approval of this application.

10. PHARMACOL. CATEGORY: Antibacterial; for treatment acute cystitis (urinary track infection caused by E. coli or Staphylococcus saprophyticus)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

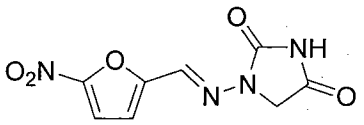
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___ SPOTS product - Form Completed

X Not a SPOTS product

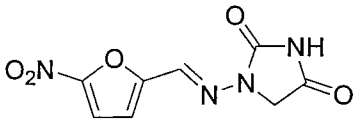
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[(5-nitrofurfurylidene)amino]hydantoin



CAS: *67-20-9*
Molecular Weight: 238.2
Molecular formula: $C_8H_6N_4O_5$

1-[(5-nitrofurfurylidene)amino]hydantoin monohydrate



.H_2O

CAS: *17140-81-7*
Molecular Weight: 256.17
Molecular formula: $C_8H_6N_4O_5$ .H_2O

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF:

DMF #	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
	II			1	Inadequate	10/02/03	Rev #2 by Dr. R. S. Randad
	II			1	Inadequate	10/01/03	Rev #3 by Dr. R. S. Randad
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III						
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

APPEARS THIS WAY ON ORIGINAL

[1] Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application

5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Related NDA/ANDA (s):

As of this review OGD has not approved ANDA for Nitrofurantoin Monohydrate/Macrocrystals combination DP. However, following ANDA's for Nitrofurantoin have been approved by OGD:

FIRM NAME	ANDA #	STRENGTH	STATUS	DATE
Ivax	73-652	100 mg	Approved	01/28/93
Ivax	73-671	50 mg	Approved	01/28/93
Watson	73-696	25, 50, 100 mg	Approved	12/31/92
Geneva	74-336	25, 50, 100 mg	Approved	01/25/95
Mylan	74-967	50 mg, 100 mg	Approved	07/09/97
Lannett	80-017	Tab	Approved	09/30/70
Eon	80-043	tab	Approved	11/25/70

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	03/24/03	J. D. Ambrogio (HFD 322)
Methods Validation	Not issued (see item 31)		
Labeling	Acceptable	9/9/03	R. Wu
Bioequivalence	Deficient	10/27/03	D. Patel
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _____ Yes __X__ No
If no, explain reason(s) below:

MINOR AMENDMENT

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-648

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #76-648 is not approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance Nitrofurantoin Monohydrate is lemon-yellow powder, and Nitrofurantoin Macrocrystals is Brown-yellow crystalline powder. The

- The drug substance exists in two polymorphic forms, anhydrous Macrocrystals and Monohydrate. Firm controls for these forms with specifications NMT and between , of respectively.

- The drug product, Nitrofurantoin Monohydrate/Macrocrystals (75/25) is available as 100 mg capsules . Each capsule contains twenty-five (25%) percent of Nitrofurantoin Macrocrystals, which has slower dissolution and absorption than Nitrofurantoin Monohydrate and the remaining 75% is Nitrofurantoin Monohydrate.

- The DP formulation is as follows: Nitrofurantoin Monohydrate as extended release, and Nitrofurantoin Macrocrystals as immediate release.

- The capsule have a light gray Opaque cap and light brown Opaque body. Each hard shell gelatin capsule is filled with one orange Nitrofurantoin Macrocrystals and two yellow round flat face Nitrofurantoin Monohydrate tablets with no markings.

- Nitrofurantoin Monohydrate/Macrocrystals capsules is labeled for an oral use. Mylan's Nitrofurantoin Monohydrate/ Macrocrystals are dispensed in bottles of 100 and 500 capsules. The beige HDPE bottles and closure with ——— meet the requirement as well-closed containers.

- The drug substance (DS) is an official article. Firm's analytical methods are based upon current USP and they are satisfactory.

- The drug product (DP) combination (75/25) is not listed in the current USP. Firm has developed validated methods to control ID, related compounds, strength, quality and purity of DP and they are satisfactory. There are some minor issues regarding the manufacturing control that need to be resolved.

- The acceptability of the current dissolution specifications are contingent up on the acceptance by the Division of Bioequivalence (DBE).

B. Description of How the Drug Product is Intended to be Used

- The dose for the Nitrofurantoin Monohydrate/Macrocrystal capsules should be individualized. The recommended dose for adults and pediatric patients over 12 years is one 100 mg every 12-hours for seven days. The Nitrofurantoin Monohydrate /Macrocrystals capsule should be taken with food.

- Tablets are to be stored under the CRT 15-30^{0}C (59-86 ^{0}F) and dispensed in a tight, light resistant containers. The expiration dating for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- Minor CMC issue
- Bio-equivalency deficient

III. Administrative

A. Reviewer's Signature

RS Randad

Ramnarayan S. Randad

B. Endorsement Block

RS Randad 12/10/03

HFD-620/Ramnarayan S. Randad, Ph.D./
HFD-620/Shing Liu, Team Leader/ S.H.Liu 12/10/03
HFD-617/Wanda Pamphile, Pharm. D./ WP 12/10/03

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C. CC Block

ANDA 76-648
ANDA DUP
DIV FILE
Field Copy

Chemistry Assessment

Comment about Telephone Amendment dated October 07, 2003

This amendment is submitted to revise the in-process tap-density specifications for Nitrofurantoin Monohydrate formulation from [redacted] The revision is based on the [redacted] data obtained from the [redacted] production size batches [redacted]. Firm states that the [redacted] meets criteria for the appearance, moisture, and [redacted] Firm has provided revised in-process specifications. This is acceptable.

Comment about Minor Amendment dated September 5, 2003

NOTE: This amendment is submitted in response to the agencies deficiency letter dated July 9, 2003. Firm has satisfactorily responded to all deficiencies (except DMF), firms response is summarized below. The revised specifications as result of this amendment are included in their respective sections.

As a result of this amendment following revision were made to the ANDA to address agencies concerns:

- DS specifications
- In-process specifications
- FP specifications, and
- stability specifications, and
- analytical method

FDA Deficiency 1. DMF's [redacted] for the [redacted] respectively, have been found inadequate. The DMF holders have been informed. Please notify in your response that the holders have responded to the deficiencies.

Firms response: Satisfactory.
Firm states that they have been notified by the manufacturer that amendment has been submitted to address all deficiencies. Both DMF's were reviewed (12/05/03) and were found to be inadequate.

FDA Deficiency 2. Please revise the specifications for the Nitrofurantoin Macrocrystals to:

a. include limit for related [redacted] and

Redacted 17

Page(s) of trade secret and /or confidential commercial information

ANDA 76-648

Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg

Mylan Pharmaceuticals, Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-648

2. REVIEW #: 03

3. REVIEW DATE: February 16, 2004
   Revision date: February 19, 2004

4. REVIEWER: Ramnarayan S. Randad

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Mylan:	
Original submission	January 28, 2003
NC	May 27, 2003
Amendment (Labeling)	August 13, 2003
Minor Amendment	September 05, 2003
Telephone Amendment (Gratuitous)	October 07, 2003

FDA:	Document Date
Acknowledgement letter (acceptable for filling: 01/29/03)	March 10, 2003
Deficiency letter	July 09, 2003
Deficiency letter	December 10, 2003
Telephone Amendment request	February 04, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment & Bio Amdt.	February 12, 2004
Minor Amendment	December 12, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharamceutical, Inc.
Address:	781 Chestnut Ridge Road, P. O. Box 4310, Morgantown, WV 26504-4310
Representative:	Frank R. Sisto
Telephone:	304-599-2595
FAX:	304-285-6407

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Nitrofurantoin Monohydrate/ Macrocrystals

9. LEGAL BASIS FOR SUBMISSION: 505(j) Satisfactory Rev. #1

Reference Product: Macrobid® (Nitrofurantoin Monohydrate/Macrocrystals). 100 mg Capsule contains 75 mg of Nitrofurantoin Monohydrate & 25 mg of Nitrofurantoin Macrocrystals
Manufacturer: Proctor & Gamble
NDA # 020064

	Patent #	Expiration Date	Use Code
Patent	4,772,473 and 4,798,725	June 16, 2006	
Exclusivity	None		

10. PHARMACOL. CATEGORY: Antibacterial; for treatment acute cystitis (urinary track infection caused by E. coli or Staphylococcus saprophyticus)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

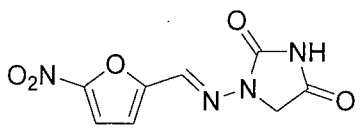
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___SPOTS product – Form Completed
X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[(5-nitrofurfurylidene)amino]hydantoin



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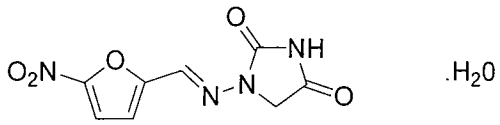
Molecular Weight: 238.2
Molecular formula: $C_8H_6N_4O_5$

1-[(5-nitrofurfurylidene)amino]hydantoin monohydrate



CAS: *17140-81-7*
Molecular Weight: 256.17
Molecular formula: $C_8H_6N_4O_5 .H_2O$

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF:

DMF #	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
	II			1	Adequate	1/6/04	Rev #3 by Dr. R. S. Randad
	II			1	Adequate	1/6/04	Rev #4 by Dr. R. S. Randad
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III						
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
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	III			4	N/A		

APPEARS THIS WAY ON ORIGINAL

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6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Related NDA/ANDA (s):

As of this review OGD has not approved ANDA for Nitrofurantoin Monohydrate/Macrocrystals combination DP. However, following ANDA's for Nitrofurantoin have been approved by OGD:

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Geneva	74-336	25, 50, 100 mg	Approved	01/25/95
Mylan	74-967	50 mg, 100 mg	Approved	07/09/97
Lannett	80-017	Tab	Approved	09/30/70
Eon	80-043	tab	Approved	11/25/70

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	03/24/03	J. D. Ambrogio (HFD 322)
Methods Validation	Not issued (see item 31)		
Labeling	Acceptable	9/9/03	R. Wu
Bioequivalence	Acceptable	1/29/04	D. Patel
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _____ Yes __X__ No
If no, explain reason(s) below:

MINOR AMENDMENT

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-648

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #76-648 is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance Nitrofurantoin Monohydrate is lemon-yellow powder, and Nitrofurantoin Macrocrystals is Brown-yellow crystalline powder.

- The drug substance exists in two polymorphic forms, anhydrous Macrocrystals and Monohydrate. Firm controls for these forms with specifications NMT and between of respectively.

- The drug product, Nitrofurantoin Monohydrate/Macrocrystals (75/25) is available as 100 mg capsules . Each capsule contains twenty-five (25%) percent of Nitrofurantoin Macrocrystals, which has slower dissolution and absorption than Nitrofurantoin Monohydrate and the remaining 75% is Nitrofurantoin Monohydrate.

- The DP formulation is as follows: Nitrofurantoin Monohydrate as extended release, and Nitrofurantoin Macrocrystals as immediate release.

- The capsule have a light gray Opaque cap and light brown Opaque body. Each hard shell gelatin capsule is filled with one orange Nitrofurantoin Macrocrystals and two yellow round flat face Nitrofurantoin Monohydrate tablets with no markings.

- Nitrofurantoin Monohydrate/Macrocrystals capsules is labeled for an oral use. Mylan's Nitrofurantoin Monohydrate/ Macrocrystals are dispensed in bottles of 100 and 500 capsules. The beige HDPE bottles and closure with [redacted] meet the requirement as well-closed containers.

- The drug substance (DS) is an official article. Firm's analytical methods are based upon current USP and they are satisfactory.

- The drug product (DP) combination (75/25) is not listed in the current USP. Firm has developed validated methods to control ID, related compounds, strength, quality and purity of DP and they are satisfactory. There are some minor issues regarding the manufacturing control that need to be resolved.

B. Description of How the Drug Product is Intended to be Used

- The dose for the Nitrofurantoin Monohydrate/Macrocrystal capsules should be individualized. The recommended dose for adults and pediatric patients over 12 years is one 100 mg every 12-hours for seven days. The Nitrofurantoin Monohydrate /Macrocrystals capsule should be taken with food.

- Tablets are to be stored under the CRT 15-30^{0}C (59-86 ^{0}F) and dispensed in a tight, light resistant containers. The expiration dating for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable, CMC, Labeling and Bioequivalency, and EER are all acceptable.

APPEARS THIS WAY
ON ORIGINAL

III. Administrative

A. Reviewer Ramnarayan S. Randad

B. Endorsement Block

HFD-620/Ramnarayan S. Randad, Ph.D./ 3/9/04
HFD-620/Shing Liu, Team Leader/ S. H. Liu 3/10/04
HFD-617/Wanda Pamphile, Pharm. D./

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C. CC Block

ANDA 76-648
ANDA DUP
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APPEARS THIS WAY
ON ORIGINAL

Chemistry Assessment

Review of Telephone Amendment dated February 12, 2004

A telephone amendment request was made on February 04, 2004. This amendment includes:

Revised FP release and stability specifications and, dissolution data on retained samples from three month accelerated program.

The revisions are provided to incorporate the DME recommended dissolution method.

Revised dissolution method is as follows:

[redacted] at 1 hour,
[redacted] at 3 hours,
NLT [redacted] at 14 hours

Apparatus:	2(paddle) @ 100 rpm
Medium:	900 ml 0.01N HCl for fist 1 hr, then change to phosphate buffer (pH 7.5 ±0.5)
Temperature:	37^{0}C ±0.5^{0}C
Sampling time:	1, 3, 7, and 14 hr
Specifications:	1 hour: [redacted]
	3 hours: [redacted]
	7 hours: [redacted]
	14 hours: NLT [redacted]

The dissolution data on retained samples is satisfactory. The revisions to the specifications as result of this amendment are included in the respective sections.

Review of Minor Amendment dated December 12, 2003

This amendment is submitted in response to the agencies deficiency letter dated December 10, 2003. Firm has responded to all deficiencies, firms response is summarized below. The revisions to the specifications as result of this amendment are included in the respective sections.

FDA Deficiency 1. DMF's # [redacted] respectively, have been found inadequate. The DMF holder has been informed. Please notify in your response that the holder has responded to the deficiencies.

Redacted 14

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-648

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-648
Drug Product Name	Nitrofurantoin monohydrate /Macrocrystalline Nitrofurantoin Capsule
Strength	(75mg/25mg) = 100 mg
Applicant Name	Mylan Pharmaceuticals, Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504-4310
Submission Date(s)	January 28, 2003
Amendment Date(s)	None
Reviewer	Devvrat Patel
First Generic	No
File Location	v:\firmsam\mylan\ltrs&rev\76648N0103.doc

I. Executive Summary

This application references Macrobid® capsule and includes one fed bioequivalence study. The fed study was a single-dose, two-way crossover study in normal healthy male and female subjects (n=68) given a dose of 100 mg. As per the protocol, the intent of the study was to complete 60 subjects. However, the firm has performed the statistical analysis (point estimate, 90% CI) on pharmacokinetic parameters determined from 68 subjects ($LAUC_{0-t}$ 1.12, 106.44-118.19%; $LAUC_{0-inf}$ 1.10, 104.68-116.18%; LC_{max} 0.86, 80.21-92.83%). Since the firm did not amend the protocol to allow for statistical analysis of data from 68 subjects, it is requested to explain this protocol deviation. The reviewer performed the statistical analysis on data from 60 subjects consisting of first 30 subjects from groups 1 and 2 completing the study. The treatment*group interaction was found not to be statistically significant. The results (point estimate, 90% CI) of the fed study are $LAUC_{0-t}$ 1.11, 104.52-117.38%; $LAUC_{0-inf}$ 1.09, 102.51-115.01%; LC_{max} 0.83, 77.14-90.15%. The fed bioequivalence study is incomplete. Additionally, the firm did not provide an explanation for reassaying all samples for subject 65. Finally, the firm has not conducted the dissolution testing using the FDA-recommended dissolution method. The firm has not met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is incomplete.

Note : The Orange Book lists the RLD as Nitrofurantoin/ Nitrofurantoin Macrocrystalline 75 mg/ 25 mg capsule. The innovator's labeling describes it as Macrobid® (nitrofurantoin/macrocrystals) capsules. Mylan's labeling describes it as Nitrofurantoin monohydrate/macrocrystals capsule 100 mg. Since the Orange Book describes the product more appropriately, it is the preferred way to describe this product.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Nitrofurantoin Monohydrate/Macrocrystals Capsules, 100 mg
Reference Product	Macrobid® Capsule, 100 mg (Composed of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate)
RLD Manufacturer	Procter and Gamble
NDA No.	20-064
RLD Approval Date	12/24/1991
Indication	Treatment of acute uncomplicated urinary tract infections caused by susceptible strains of *Escherichia coli* or *Staphylococcus saprophyticus*.

B. PK/PD Information

Bioavailability	Macrocrystalline nitrofurantoin has slower dissolution and absorption than nitrofurantoin monohydrate. Nitrofurantoin monohydrate, when exposed to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time.
Food Effect	When Macrobid® is administered with food, the bioavailability is increased by approximately 40%.
C_{max}	Nitrofurantoin plasma concentrations are low with peak levels less than 1 mcg/mL.
Metabolism	The labeling does not mention any active metabolite of nitrofurantoin
Excretion	Approximately 20% to 25% of nitrofurantoin is recovered from the urine unchanged over 24 hours following a single, oral dose.
Half-Life	According to clinical study submitted in the NDA, the elimination half-life was approximately 0.76 hours.

Relevant OGD or DBE History

Nitrofurantoin is also available as Macrodantin® (nitrofurantoin macrocrystalline) capsules 25 mg, 50 mg and 100 mg strengths (NDA 16620) and as Furadantin® (nitrofurantoin for oral suspension) 25 mg/5 mL (NDA 009175).

In the bioequivalence studies of nitrofurantoin macrocrystalline 100 mg capsules, ANDA 74-967 (Mylan, submission date: 4/26/1996) and ANDA 74-336 (Geneva, submission date: 3/30/1993), the assays were based on the nitrofurantoin urine samples.

The bioequivalence studies of the ANDAs 73-652 (Zenith Labs, submission date: 10/12/1990), 73-671 (Zenith, submission date: 12/7/1990), 73-696 (Danbury, submission date: 12/14/1990), 74-336 (Geneva, submission date: 3/30/1993) and 74-967 (Mylan, submission date: 9/24/1996) were conducted under non-fasting conditions only and were found acceptable.

Currently, the DBE recommends only non-fasting bioequivalence study for nitrofurantoin (Lachman, Control document 00-490, submission date: 11/14/2000).

The DBE has not reviewed any nitrofurantoin monohydrate/macrocrystals capsule ANDAs.

The DBE reviewed a protocol on the proposed bioequivalence study on nitrofurantoin monohydrate/macrocrystals capsule, 100 mg (Mylan, 01010P.201, submission date: 2/14/2001). The protocol proposed measuring plasma levels of nitrofurantoin using [redacted] procedures developed by the sponsor. The protocol has been found acceptable to the DBE.

The DBE recommends the following NDA (20064) method for the dissolution testing:

Medium: 0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume: 900 mL
Apparatus: USP 2 (Paddle) at 100 rpm

Sampling times: 1, 3 and 7 hours
Specifications: 1 hour: Mean
Individual
3 hours: Mean
Individual
7 hours: Mean NLT
Individual NLT

Agency Guidance N/A
Drug Specific Issues (if any) N/A

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	
Internal Standard	
Method description	
QC range	
Standard curve range	
Limit of quantitation	
Average recovery of Drug (%)	
Average Recovery of Int. Std (%)	
Intraday precision range (%CV)	
Intraday accuracy range (%)	
Interday precision range (%CV)	
Interday accuracy range (%)	
Bench-top stability (hrs)	
Stock stability (days)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	
Specificity	
SOPs submitted	
Bioanalytical method is acceptable	
20% Chromatograms included (Y/N)	
Random Selection of Serial Chromatograms	

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Not applicable (Fasting study is not required for this drug product).

2. Single-dose Fed Bioequivalence Study

Study No.	NITF-02103
Study Design	Randomized, Single dose, Two way, Crossover
No. of subjects enrolled	71
No. of subjects completing	68
No. of subjects analyzed	60
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 53 Female: 7
Test product	Nitrofurantoin Monohydrate/Macrocrystals Capsule
Reference product	Macrobid® Capsule
Strength tested	100 mg containing 75 mg of Nitrofurantoin Monohydrate and 25 mg of Nitrofurantoin Macrocrystals
Dose	1 x 100 mg capsule

Summary of Statistical Analysis* **Additional Information in Appendix, Table 7 and Table 8**		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$	1.12	106.44 – 118.19
$LAUC_{0-\infty}$	1.10	104.68 – 116.18
LC_{max}	0.86	80.21 – 92.83

*Based on data from 68 subjects

Reanalysis of Study Samples **Additional information in Appendix, Table 6**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays[1]**		**Actual number**		**% of total assays[1]**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Analytical repeats	101	100	2.5	2.5	101	100	2.5	2.5
Pharmacokinetic repeats	0	0	0	0	0	0	0	0
Total	**101**	**100**	**2.5**	**2.5**	**101**	**100**	**2.5**	**2.5**

[1] Based on total number of samples analyzed: 4080

Did use of recalculated plasma concentration data change study outcome? No.

Comments on fed study: The study is incomplete because the firm deviated from the protocol with regards to the number of subjects used to establish bioequivalence. As per the protocol, the intent of the study was to complete 60 subjects. The firm conducted the statistical analysis on data from 68 subjects completing the study.

F. Formulation

Location in appendix	Section B, Page 21
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	No
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	0.01 N HCl for the first hour followed by the addition of 50 mL of sodium phosphate tribasic dodecahydrate solution, final pH 7.5 ± 0.05 for 13 hours at 37 °C ± 0.5 °C
Volume (mL)	900 mL
USP Apparatus type	Apparatus 1 (Basket), [redacted]
Rotation (rpm)	100 rpm
Firm's proposed specifications	1 hour: NMT [redacted] 10 hours: [redacted] 14 hours: NLT [redacted]
FDA-recommended specifications (NDA method)	1 hour: Mean [redacted], Individual [redacted] 3 hours: Mean [redacted], Individual [redacted] 7 hours: Mean NLT [redacted] Individual NLT [redacted]
F2 metric calculated (yes or no)	Yes
If no, reason why F2 not calculated	N/A
Method is acceptable (yes or no)	No

F2 metric, other strengths compared to biostudy strength			
Low strength	**Highest strength**	**F2 metric for test**	**F2 metric for RLD**
Not Applicable			

F2 metric, test compared to reference	
Strength	**F2 metric**
100 mg	28.91

H. Waiver Request(s)

Strengths for which waivers requested	N/A
Regulation cited	N/A
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	N/A
Waiver granted (yes or no)	N/A

I. Deficiency Comments

1. As per the study protocol, the intent of the fed bioequivalence study was to complete 60 subjects. From inception of the protocol to completion of the study, the firm has not amended the protocol with regards to the number of subjects needed for establishing bioequivalence. Therefore, although 68 subjects (including the alternates) completed the study, the statistical analysis should have been performed on data from 60 subjects as indicated in the protocol. The firm has performed the statistical analysis on pharmacokinetic parameters determined from 68 subjects. The firm should explain this protocol deviation.

2. The firm stated that all samples for subject 65 were reassayed because the "subject was lost during assay procedure", which was not clearly explained. The firm should provide detailed explanation for reassaying the whole subject profile.

3. The firm has not conducted the dissolution testing using the FDA-recommended dissolution method (NDA method). The firm should be advised to conduct the dissolution testing using the following method:

Medium:	0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume:	900 mL
Apparatus:	USP 2 (Paddle) at 100 rpm
Sampling times:	1, 3 and 7 hours

J. Recommendations

1. The *in vivo* bioequivalence study conducted under fed conditions by Mylan on its nitrofurantoin monohydrate/macrocrystals 100 mg capsule, comparing it to the reference product Macrobid® 100 mg capsule (Procter & Gamble) is incomplete because of the deficiencies mentioned above.

2. The firm stated that all samples for subject 65 were reassayed because the "subject was lost during assay procedure". This reason was not explained in the Reassay of Whole Subjects SOP (D-416-01). The firm should provide detailed explanation for reassaying the whole profile for this subject.

3. The dissolution testing conducted by Mylan on its nitrofurantoin monohydrate/macrocrystals 100 mg capsule is incomplete. The dissolution testing should be performed using the following FDA-recommended method:

Medium:	0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume:	900 mL
Apparatus:	USP 2 (Paddle) at 100 rpm
Sampling times:	1, 3 and 7 hours

4. The firm has not met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is incomplete.

Devrat Patel 10/24/2003

Devvrat Patel, Pharm.D. Date Signed
Division of Bioequivalence, Branch II

10/24/2003

Shriniwas Nerurkar, Ph.D. Date Signed
Team Leader, Division of Bioequivalence, Branch II

Barbara M Davit 10/24/03

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Not Applicable (Fasting study is not required for this drug product).

2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	NITF-02103
Study Title	Single-Dose Food In Vivo Bioequivalence Study of Nitrofurantoin Monohydrate/Macrocrystals Capsules (100 mg; Mylan) and Macrobid® Capsules (100 mg; Procter & Gamble) in Healthy Volunteers
Clinical Site	[redacted]
Principal Investigator	[redacted]
Study/Dosing Dates	Group 1: 10/25/2002 to 11/03/2002 Group 2: 11/08/2002 to 11/17/2002 Dosing Dates: Group 1: Period 1: 10/26/2002; Period 2: 11/02/2002 Group 2: Period 1: 11/09/2002; Period 2: 11/16/2002
Analytical Site	Mylan Pharmaceuticals, Bioanalytical Department 3711 Collins Ferry Rd, Morgantown, WV 26505
Analytical Director	Sandra Tarr
Analysis Dates	11/26/2002 to 12/20/2002
Storage Period (no. of days from first sample to final analysis)	55 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Nitrofurantoin Monohydrate/Macrocrystals Capsules	Macrobid® Capsules
Manufacturer	Mylan Pharmaceuticals	Procter & Gamble
Batch/Lot No.	R1K1068	CN371363
Manufacture Date	03/25/2002	N/A
Expiration Date	N/A	01/2004
Strength	100 mg	100 mg
Dosage Form	Capsule	Capsule
Batch Size	[redacted] capsules	N/A
Production Batch Size	[redacted] capsules	N/A
Potency	97.3%	98.8%
Content Uniformity	97.8%; %CV: 1.1	98.0%; %CV: 0.9
Formulation	See Appendix Section B	
Dose Administered	100 mg	100 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	AB: 2, 3, 5, 7, 8, 11, 13, 16, 17, 20, 21, 24, 25, 26, 28, 29, 34, 35, 37, 42, 43, 44, 46, 47, 50, 51, 53, 55, 58, 59, 64, 65, 66, 67, 70, 72 BA: 1, 4, 6, 9, 10, 12, 14, 15, 18, 19, 22, 23, 27, 30, 32, 33, 36, 38, 39, 40, 41, 45, 48, 49, 52, 54, 56, 57, 60, 61, 62, 63, 68, 69, 71
Blood Sampling Times	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 23, 24, 25, 26, 28, 29, 30, 32, 34 and 36 hours post-dose
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	Blood samples were collected in heparinized tubes. Samples were centrifuged at 3000 rpm for 10 minutes under refrigeration. Plasma was extracted and transferred into polypropylene tubes and stored at -70±15 °C, until analysis.
IRB Approval	Yes
Informed Consent	Yes

Subjects Demographics	See Table 11
Length of Fasting	Subjects fasted overnight for at least 10 hours until 30 minutes prior to their scheduled dosing times, when they were given a standard breakfast.
Length of Confinement	Subjects were confined to the clinic for at least 16 hours prior to drug administration until 36 hours post-dose.
Safety Monitoring	Clinical laboratory evaluations and 12-lead ECG were performed at screening. Vital signs were measured prior to drug administration and 24 hours post-dose. Subjects were monitored throughout confinement for adverse reactions.

Table 1 Demographics of Study Subjects

Age (years)		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
N	68	N	68	<18	0			Caucasian	66.2
Mean	25.0	Mean	74.2	18-40	94.1	Male	77.9	Afr. Amer.	23.5
SD	7.1	SD	11.2	41-64	5.9	Female	22.1	Hispanic	7.4
Min	18	Min	53.6	65-75	0			Asian	0
Max	53	Max	102.3	>75	0			Others	2.9

Study Results

Table 2 Dropout Information

Subject No	29
Reason	Adverse event
Period	During Group 1, Period 1
Replacement	No

Subject No	70
Reason	Adverse event
Period	Prior to Group 2, Period 2
Replacement	No

Subject No	72
Reason	Adverse event
Period	During Group 2, Period 2
Replacement	No

Was there a difference in side effects for the test versus the reference? No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Dizziness	1	0
Nausea	1	1
Headache	4	2
Rapid heartbeat	1	0
Blood in urine	0	1
Pain at heparin lock site	1	0
Chills	1	0
Congestion	1	0
Pressure in right ear	1	0
Tingling sensation in fingers	1	0
Lightheadedness	1	0
Vomiting	0	3
Total:	**13**	**7**

Comments: (*on adverse events)*

There were 20 adverse events experienced by 9 subjects in this study. Eighteen adverse events were categorized as mild in severity and 2 were listed as moderate in severity. Thirteen adverse events were listed as possibly related to the study drug, 4 were listed as remotely related to the study drug and 3 were listed as unrelated to the study drug. No serious adverse events occurred during the conduct of the study.

Subject 72 vomited three times 7 hours after dosing. Blood samples for this subject were not analyzed since the subject was discontinued from the study due to adverse events.

Was there a difference in protocol deviations for the test versus the reference? No

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Reference)
Subject dropped out of the study in period 1 and refused to remain at the study unit for 36 hours after dosing. Subject did not report for complete post-study evaluation	29	--
Subject self-administered one aspirin tablet for an adverse event experience.	56	--

Comments: (protocol deviations)

Blood samples, which were collected within 2 minutes of scheduling time, were not considered as protocol deviations. The firm did not report any blood collection time deviations.

Table 5 Assay Validation – Within Study

	Parent
QC Conc. (ng/mL)	[redacted]
Inter day Precision (%CV)	
Inter day Accuracy (% Accuracy)	
Cal. Standards Conc. (ng/mL)	
Inter day Precision (%CV)	
Inter day Accuracy (%)	
Linearity Range (range of R^2 values)	

Chromatograms: Any interfering peaks? No

Table 6 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
D-400-02	09/24/2002	Reassay or Reinjection of Clinical Samples
D-401-04	04/21/2002	Evaluation and Acceptance Criteria for Standard Curves, Quality Controls and Biostudy Sample Batches
D-416-01	06/18/2002	Reassay of Whole Subjects

Comments on Repeat Assays:

All of the samples for subjects 58, 65 and 27 were reassayed due to unacceptable controls, subject lost during assay procedure and unacceptable standard curve, respectively. The firm stated that all samples for subject 65 were repeated because the subject was lost during assay procedure. The Reassay of Whole Subjects SOP (D-416-01) did not indicate this as one of the criteria for identifying situations in which whole subject profiles would be reassayed. The firm should provide an explanation for reassaying all of the samples for subject 65.

Repeat analyses were conducted on 201 samples due to analytical abnormalities. There were no pharmacokinetic repeats. Re-assayed samples represented 5.0% of the total 4080 plasma samples assayed.

The samples were reanalyzed and reported according to the SOP.

Comments on Within-Study Validation: None

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figure 1

Data from 68 subjects completing the study were used for the determination of pharmacokinetic parameters and statistical analysis.

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUCI	ng·hr/mL	1906.13	24.84	1725.05	22.94	1.10
AUCT	ng·hr/mL	1892.15	24.84	1688.37	24.24	1.12
CMAX	ng/mL	427.72	32.29	493.32	30.38	0.87
KE	$hour^{-1}$	1.03	23.59	1.03	24.38	1.00
LAUCI	ng·hr/mL	1850.78	0.01	1677.37	0.01	1.10
LAUCT	ng·hr/mL	1837.10	0.01	1635.59	0.02	1.12
LCMAX	ng/mL	406.63	0.08	471.49	0.07	0.86
THALF	hour	0.72	29.90	0.75	54.34	0.95
TMAX	hour	6.69	46.42	7.75	60.25	0.86

Table 8 Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUCI	1901.40	1719.74	1.11	105.24	115.88
AUCT	1892.27	1689.94	1.12	106.72	117.22
CMAX	428.62	493.73	0.87	80.08	93.54
LAUCI	1846.60	1674.48	1.10	104.68	116.18
LAUCT	1836.60	1637.42	1.12	106.44	118.19
LCMAX	407.24	471.94	0.86	80.21	92.83

Note: Log-transformed data were converted to anti-log in the table

Table 9 Additional Study Information

Root mean square error, AUC_{0-t}	0.183	
Root mean square error, $AUC_{0-\infty}$	0.176	
Root mean square error, C_{max}	0.255	
mean ratio $AUC_{0-t}/AUC_{0-\infty}$	**T** = 0.99	**R** = 0.99
Range of values, ratio $AUC_{0-t}/AUC_{0-\infty}$	**T** = 0.98 to 1.00	**R** = 0.97 to 1.00

Comments: (on pharmacokinetic analysis)

- According to the protocol, the study was intended to include sufficient number of subjects in order to complete 60 subjects. The sponsor was planning to complete all subjects simultaneously. As per the study report, 35 subjects (including 3 alternates) were dosed in group 1, and 36 subjects (including 3 alternates) were dosed in group 2. A total of 68 subjects completed the study; 34 subjects completed group 1, and 34 subjects completed group 2.

  Samples from 68 subjects completing the study were assayed, and the firm performed statistical analysis on the pharmacokinetic parameters determined for all of the subjects completing the study. Since the study was performed in two groups, the firm analyzed the data with the group effect incorporated in the ANOVA model. The reviewer calculated the pharmacokinetic parameters and their 90% confidence intervals. After including the group factor in the statistical analysis, the treatment*group interaction was found not to be statistically significant for log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. The treatment*group interaction was taken out of the statistical model. The following model was used in PROC GLM procedure:

  MODEL AUCT AUCI CMAX LAUCT LAUCI LCMAX = GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT

  The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} (68 subjects) are within acceptable limits of 80-125% ($LAUC_{0-t}$ 106.44-118.19; $LAUC_{0-inf}$ 104.68-116.18; LC_{max} 80.21-92.83).

- Since the intent of the study was to complete 60 subjects as per the protocol, the firm should have analyzed the data of 60 subjects completing the study. The reviewer calculated the pharmacokinetic parameters and their 90% confidence intervals using data from 60 subjects consisting of first 30 subjects from group 1, and first 30 subjects from group 2.

  After including the group factor in the statistical analysis, the treatment*group interaction was found not to be statistically significant for log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. The treatment*group interaction was taken out of the statistical model and the model mentioned above was used in the PROC GLM procedure.

The reviewer calculated 90% confidence intervals for $LAUC_{0-t}$ and $LAUC_{0-inf}$ are within acceptable limits of 80-125% ($LAUC_{0-t}$ 104.52-117.38%; $LAUC_{0-inf}$ 102.51-115.01%). The lower limit of the 90% confidence intervals for LC_{max} is outside the acceptable limit of 80% (LC_{max} 77.14-90.15%).

- Additionally, the reviewer recalculated the pharmacokinetic parameters and their 90% confidence intervals using data from first 60 subjects completing the study. Similar results were obtained ($LAUC_{0-t}$ 103.87-116.31%; $LAUC_{0-inf}$ 101.86-113.86%; LC_{max} 76.73-88.08%). The 90% confidence intervals for LC_{max} are outside the acceptable limits of 80-125%.

- It should be noted that according to the plasma concentration-time profiles, 9 subjects (4 test, 5 reference) had second peak between 10 to 25 hours post-dose. This seems to be a characteristic of the active drug substance since it was observed in subjects receiving test and reference products. The immediate-release component, nitrofurantoin macrocrystalline, provides rapid availability of the active ingredient. The modified-release component, nitrofurantoin monohydrate, is contained in powder blend which, upon exposure to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time. The modified release formulation may have resulted in the second peak.

- The sequence and the period effects were not statistically significant for any of the pharmacokinetic parameters. The treatment was statistically significant for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.

- K_{el} and AUC_{0-inf} were determined for 64 subjects who completed the study (periods 1 and 2).

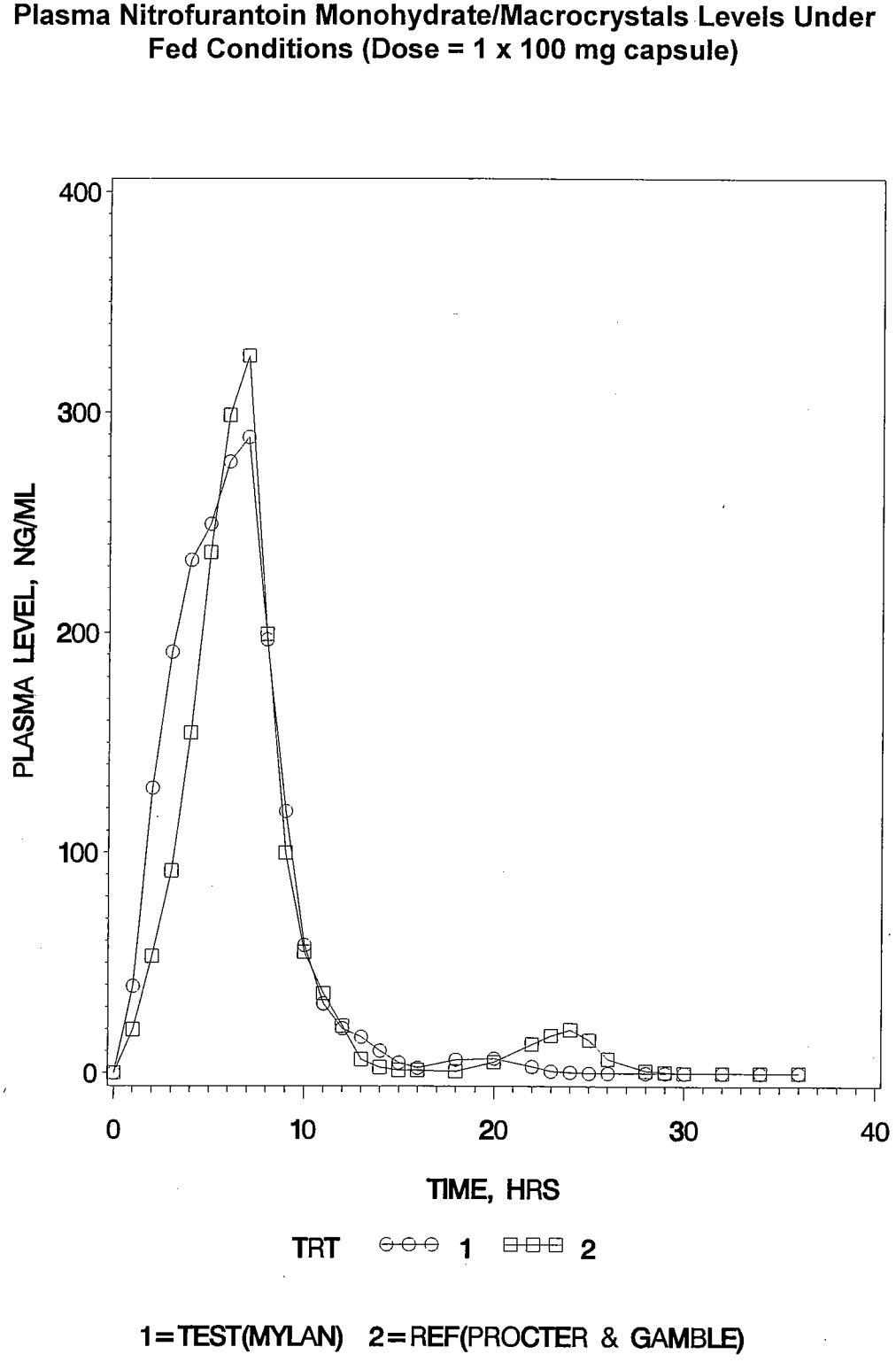
- Number of subjects with the following:
  a. Measurable drug concentrations at 0 hr: None
  b. First scheduled post-dose sampling time as T_{max}: None
  c. First measurable drug concentration as C_{max}: None

Conclusion: The single-dose fed bioequivalence study is incomplete because of the deficiencies mentioned above.

Table 10 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

TIME (HR)	TEST (N=68)		REFEREENCE (N=68)		RATIO T/R
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV	
0	0.00	.	0.00	.	.
1	39.29	175.90	19.62	151.87	2.00
2	129.39	79.00	52.94	58.22	2.44
3	191.27	67.22	91.66	95.05	2.09
4	232.83	52.22	154.56	94.38	1.51
5	249.26	51.42	236.28	76.68	1.05
6	277.55	48.20	298.69	56.29	0.93
7	288.71	54.41	325.56	66.58	0.89
8	196.75	79.77	199.24	82.42	0.99
9	118.77	104.06	99.79	98.43	1.19
10	57.89	125.78	54.79	145.54	1.06
11	31.47	187.85	36.13	242.91	0.87
12	20.13	309.31	21.29	309.04	0.95
13	16.31	390.89	6.16	225.53	2.65
14	10.10	486.91	2.53	231.61	4.00
15	4.69	434.51	1.24	353.17	3.77
16	2.32	382.09	1.25	309.87	1.86
18	6.07	700.90	0.72	412.62	8.42
20	6.63	646.15	4.96	540.94	1.34
22	2.92	743.35	13.07	421.08	0.22
23	0.84	824.62	17.00	398.24	0.05
24	0.34	824.62	19.62	504.70	0.02
25	0.00	.	14.94	543.12	0.00
26	0.00	.	6.40	593.76	0.00
28	0.00	.	1.02	629.90	0.00
29	0.00	.	0.44	633.47	0.00
30	0.00	.	0.00	.	.
32	0.00	.	0.00	.	.
34	0.00	.	0.00	.	.
36	0.00	.	0.00	.	.

Figure 1 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Formulation of Nitrofurantoin Monohydrate/Macrocrystals Capsule, 100 mg

Ingredients	mg/Capsule	% (w/w)
Nitrofurantoin Monohydrate Formulation		
Nitrofurantoin, USP (Monohydrate)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Sodium Alginate, NF	[redacted]	[redacted]
Alginic Acid, NF	[redacted]	[redacted]
Microcrystalline Cellulose, NF	[redacted]	[redacted]
Dibasic Calcium Phosphate, USP Anhydrous	[redacted]	[redacted]
Magnesium Stearate, NF	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Total Theoretical Weight (of monohydrate formulation)	**400.0**	--
Nitrofurantoin Macrocrystals Formulation		
Nitrofurantoin, USP (Anhydrous Macrocrystals)	25.0	4.17
Microcrystalline Cellulose, NF	[redacted]	[redacted]
Lactose Monohydrate, NF	[redacted]	[redacted]
FD&C Yellow #6 Lake HT	[redacted]	[redacted]
Magnesium Stearate/Sodium Lauryl Sulfate	[redacted]	[redacted]
Total Theoretical Weight (of macrocrystal formulation)	**200.0**	--
Total Theoretical Weight	**600.0**	**100.0**
[redacted]		
Red Iron Oxide	[redacted]	--
Titanium Dioxide, USP	[redacted]	--
Yellow Iron Oxide	[redacted]	--
Black Iron Oxide	[redacted]	--
Gelatin, NF	[redacted]	--
Imprinting Ink	[redacted]	--

[1] Equivalent to 75 mg of nitrofurantoin /capsule
[2] Not included in the theoretical weight. [redacted]

Product Description

Product	Description
Test	Light gray opaque cap and light brown opaque body imprinted with "MYLAN" in black ink on cap and body.
Reference	Black and yellow opaque capsule imprinted with "Macrobid" on one half and "Norwich Eaton" on the other half.

Comments (Formulation)

All inactive ingredients are within the IIG limits.

C. Dissolution Data

Method:	Firm
Medium:	900 mL of 0.01 N HCl for the first hour followed by the addition of 50 mL of sodium phosphate tribasic dodecahydrate solution, final pH 7.5 ± 0.05 for 13 hours at 37 °C ± 0.5 °C
Apparatus:	1 (basket), [redacted] at 100 rpm
Specifications:	1 hour: NMT [redacted] 10 hours: [redacted] 14 hours: NLT [redacted]

Table 1

Sampling Time (hour)	Nitrofurantoin Monohydrate/Macrocrystals Capsule Strength: 100 mg Lot No. R1K1068			Macrobid® Capsule Strength: 100 mg Lot No. CN371363		
	Mean	%CV	Range	Mean	%CV	Range
1	13	7.9	[redacted]	10	5.8	[redacted]
10	62	3.1	[redacted]	103	1.3	[redacted]
14	83	4.2	[redacted]	103	1.8	[redacted]

F2 Calculations:

F2 Metric, Test Compared to Reference	
Strength	**F2 metric**
100 mg	28.91

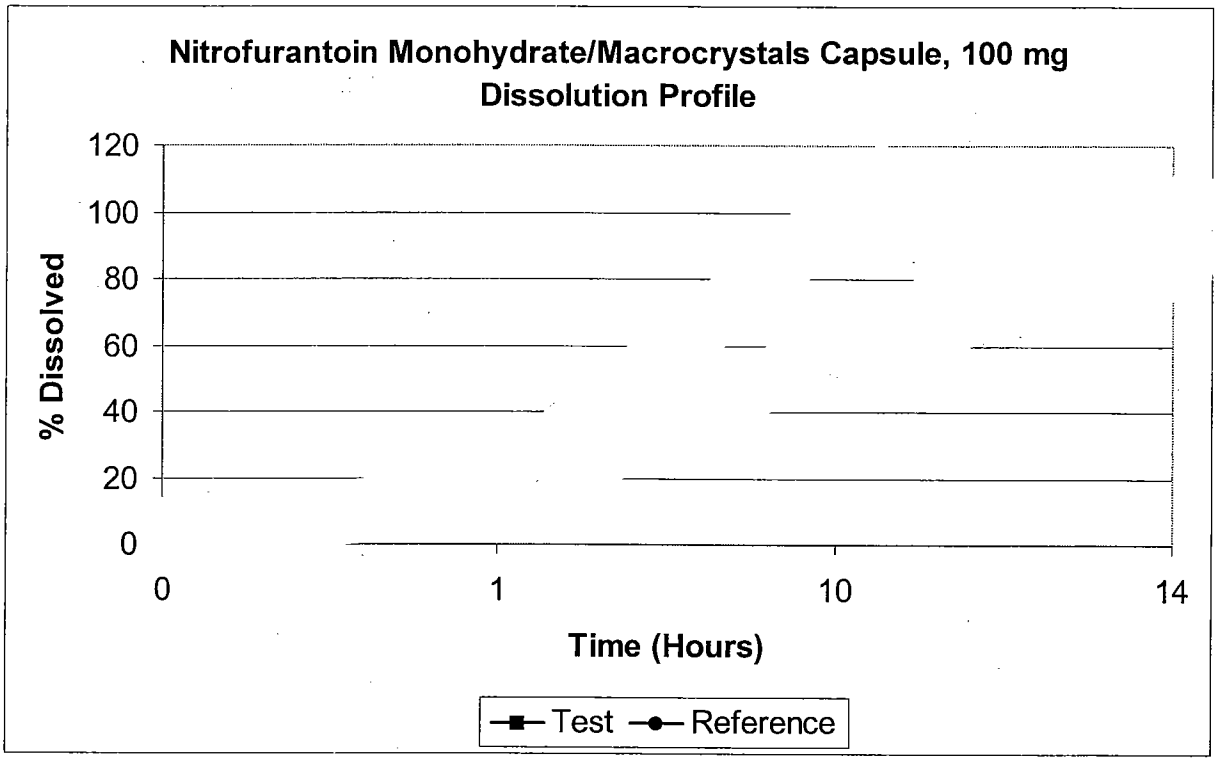
Comments (Dissolution)

The firm conducted the dissolution testing using a method that is different from the FDA recommended (NDA) method. Additionally, the FDA-recommended specifications are different compared to the firm's proposed specifications. Therefore, the dissolution testing is incomplete. The firm should be advised to conduct dissolution testing using the following method:

Medium: 0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume: 900 mL
Apparatus: USP 2 (Paddle) at 100 rpm
Sampling times: 1, 3 and 7 hours

Specifications: 1 hour: Mean [redacted]; Individual [redacted]
3 hours: Mean [redacted]; Individual [redacted]
7 hours: Mean NLT [redacted]%; Individual NLT [redacted]

Figure 2 Dissolution Profile



C. Consult Reviews

None

D. SAS Output

	Single-Dose Fed Study
SAS Program	Fed_Prog.sas
Statistical Output	Fed_Stat.txt
Plasma Concentration Data	Fed_Data.xls

E. Additional Attachments

None

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-648 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Nitrofurantoin Monohydrate/Macrocrystals Capsule, 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. As per the study protocol, the intent was to complete the fed bioequivalence study with 60 subjects and estimate bioequivalence parameters from 60 subjects. Although you did not amend the protocol to allow for statistical analysis of data from 68 subjects, you have performed the statistical analysis on data from 68 subjects completing the study. Please explain this protocol deviation.

2. In the analytical report, you stated that all samples for subject 65 were reassayed because the "subject was lost during assay procedure". This reason was not explained in the Reassay of Whole Subjects SOP (D-416-01). Please provide detailed explanation for reassaying the whole profile for this subject.

3. Please submit dissolution data on the test and reference capsules using the following method:

   Medium: 0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
   Volume: 900 mL
   Apparatus: USP 2 (Paddle) at 100 rpm
   Sampling times: 1, 3 and 7 hours

   The percentage of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percentage dissolved, the range of dissolution, and the coefficient of variation should be reported.

Sincerely yours,

Barbara M. Davit

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-648
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

Printed in final on 09/29/2003
V:\FIRMSAM\MYLAN\LTRS&REV\76648N0103.DOC

Endorsements: (Final with Dates)
HFD-655/ Patel dh 10/24/03
HFD-655/ Nerurkar
for HFD-650/ D. Conner BRD, 10/24/03

10/24/03

BIOEQUIVALENCY - INCOMPLETE Submission date: 01/28/2003

1. **FOOD STUDY** (STF) Strength: 100 mg
✓ **Outcome: IC**

Clinical:
Analytical: Mylan Pharmaceuticals, Bioanalytical Department, Morgantown, WV

Outcome Decisions: **AC** - Acceptable
IC - Incomplete
UN - Unacceptable

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-648 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Nitrofurantoin Monohydrate/Macrocrystals
Capsule, 100 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted using the following method:

Medium: 0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume: 900 mL
Apparatus: USP Apparatus 2 (Paddle) at 100 rpm
Sampling times: 1, 3, 7 and 14 hours

The specifications for your test product have been changed. The test product should meet the following specifications:

1 hour: Between [redacted]
3 hours: Between [redacted]
7 hours: Between [redacted]
14 hours: Not less than [redacted]

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 29 2004

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-648 SPONSOR : Mylan Pharmaceuticals Inc.

DRUG AND DOSAGE FORM : Nitrofurantoin Monohydrate/Macrocrystals Capsule

STRENGTH(S) : 100 mg

TYPES OF STUDIES : Fed study on nitrofurantoin monohydrate/macrocrystals capsule, 100 mg

CLINICAL STUDY SITE(S) : [redacted]

ANALYTICAL SITE(S) : Mylan Pharmaceuticals, Bioanalytical Department

STUDY SUMMARY : Fed study is acceptable.

DISSOLUTION : The dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter using USP Apparatus 2 (paddle) at 100 rpm. The test products should meet the following specifications: 1 hour: [redacted] 3 hours: [redacted] 7 hours: [redacted] 14 hours: NLT [redacted]

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic Yes	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Devvrat Patel, Pharm.D. BRANCH : II

INITIAL : Devvrat Patel DATE : 1/28/2004

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : [signature] DATE : 1/28/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [signature] DATE : 1/29/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-648

CORRESPONDENCE

MAR 10

ANDA 76-648

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

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Nitrofurantoin Monohydrate/Macrocrystals Capsules, 75 mg/25 mg

DATE OF APPLICATION: January 28, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 29, 2003

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice.

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement, or a settlement agreement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Wanda Pamphile
Project Manager
(301) 827-5848

Sincerely yours,

Gregory B. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 28, 2003

505(b)(2)OK
06-MAR-2003

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES, 100MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Nitrofurantoin Monohydrate/Macrocrystals Capsules
This application consists of a total of 25 volumes.
Archival Copy - 11 volumes.
Review Copy - 12 volumes.
Technical Section For Chemistry - 4 volumes.
Technical Section For Pharmacokinetics - 8 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application.

This application provides for the manufacture of Nitrofurantoin Monohydrate/Macrocrystals Capsules, 100mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

RECEIVED
JAN 2 5 2003
OGD / CDER

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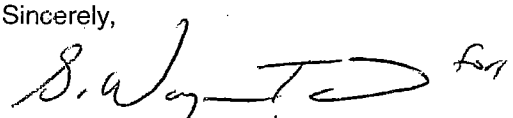
Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,



Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

APPEARS THIS WAY
ON ORIGINAL

NDA 1473+1727
RF
11/25/03

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 27, 2003

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES, 75MG/25MG
ANDA 76-648
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application (ANDA), which is currently under review. In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of the notice required by 21 CFR 314.95(a), as it pertains to the Paragraph IV patent certification contained in our original application submitted on January 28, 2003 for Nitrofurantoin Monohydrate/ Macrocrystals Capsules, 75mg/25mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patent, and the holder of the application for the listed drug was served with the required notice. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Proctor and Gamble Company and Norwich Eaton Pharmaceuticals, Inc. A copy of the documentation evidencing Mylan's service and receipt is enclosed. Mylan has not received any notice that legal action was taken within the 45-day statutory period as identified in 21 CFR 314.95(f). For this reason, Mylan believes that it is entitled to immediate effective approval of its ANDA once the regulatory requirements have been satisfied.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED
MAY 28 2003
OGD / CDER

G:\PROJECT\ANDA\NITROFURANTOIN-MACROCRYSTALS\PATENT-AMENDMENT-052703.DOC

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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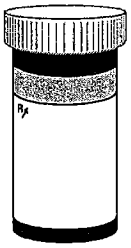
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Frank R. Sisto
Mylan Pharmaceuticals Inc.
Fax: 304-285-6407 **Phone:** 304-599-2595

From: Ruby Wu
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 3 **Date:** June 23, 2003

Comments:

Labeling comments provided for ANDA 76-648 Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100 mg.

When you submit your labeling amendment, please send a courtesy copy to my attention.

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 13, 2003

ORIG AMENDMENT,
N/AF
FPL

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
(LABELING INFORMATION ENCLOSED)

RE: NITROFURANTOIN (Monohydrate/Macrocrystals) CAPSULES
100 MG
ANDA 76-648
(RESPONSE TO AGENCY CORRESPONDENCE DATED JUNE 23, 2003)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to labeling comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated June 23, 2003 (refer to Attachment A).

The enclosed labeling incorporates the revisions requested in the Agency's correspondence dated June 23, 2003. Mylan's outsert has also been further revised pursuant to revisions in the approved labeling for the reference listed drug (RLD) product (Macrobid®), revised March 2003. Mylan obtained a copy of the innovator's labeling revisions from the RLD company's website. Copies of Agency's correspondence dated June 23, 2003 and the innovator's labeling is provided in Attachment A. Mylan also contacted Ms. Ruby Wu, of your office, on August 6, 2003 regarding the requested format of product's name and strength on the bottle labels and package outsert. Ms. Wu indicated that our proposed formatting of title was acceptable. In order to facilitate the review of this labeling, Attachment B contains a side-by-side comparison of the revised final printed bottle labels to the previously submitted draft bottle labels and Attachment C contains a side-by-side comparison of the revised final printed outsert (NTMM:R1) to the draft outsert that was previously submitted (NTMM:RX).

Attachment D contains twelve (12) copies of the following final printed bottle labels and outsert for Nitrofurantoin (Monohydrate/Macrocrystals) Capsules, 100mg.

BOTTLE LABELS

100mg
Code RM3422A - Bottles of 100 Capsules
Code RM3422B - Bottles of 500 Capsules

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AUG 14 2003
OGD/CDER

OUTSERT

Code NTMM:R1, Revised August 2003

In response to the labeling comments contained in the June 23, 2003 correspondence, Mylan wishes to amend this application as follows:

Labeling Deficiencies:

1. CONTAINER (Bottles of 100s and 500s)

FDA COMMENT 1.a: Revise the established name and strength to read:
NITROFURANTOIN (Monohydrate/Macrocrystals) CAPSULES, 100 mg*

MYLAN RESPONSE: The established name and strength were revised as follows:

NITROFURANTOIN
(Monohydrate/Macrocrystals)
CAPSULES
100 mg*

Please note that the comma after the product name was deleted and the strength was moved to the next line on the final printed bottle label, to be consistent with Mylan's standard format. This proposal was found acceptable by the Agency as discussed with Ms. Ruby Wu on August 6, 2003.

FDA COMMENT 1.b: Revise the "Each capsule" statement to read::

*Each capsule contains:

Nitrofurantoin monohydrate equivalent to 75 mg nitrofurantoin
Nitrofurantoin macrocrystals equivalent to 25 mg nitrofurantoin.

MYLAN RESPONSE: The statement of contents was revised as follows (note: USP designation was also added to the active ingredients' names):

*Each capsule contains:

Nitrofurantoin monohydrate, USP
equivalent to 75 mg nitrofurantoin

Nitrofurantoin macrocrystals, USP
equivalent to 25 mg nitrofurantoin.

2. INSERT

FDA COMMENT 2.a: GENERAL: throughout the insert, revise " ——— *" to read "nitrofurantoin macrocrystals"

MYLAN RESPONSE: As requested the brand name " ——— *" was replaced with "nitrofurantoin macrocrystals" in the following sections: "CLINICAL PHARMACOLOGY" and "CLINICAL STUDIES".

FDA COMMENT 2.b: TITLE: Revise the established name and strength to read:

NITROFURANTOIN (Monohydrate/Macrocrystals) CAPSULES, 100 mg
(Twice-a-day Dosage)

MYLAN RESPONSE: Please note that the comma after the product name was deleted and the strength was moved to the next line on the final printed package outsert, to be consistent with Mylan's standard format. This proposal was found acceptable by the Agency as discussed with Ms. Ruby Wu on August 6, 2003.

FDA COMMENT 2.c: DESCRIPTION: Inactive ingredients: revise " [redacted]" to read "hypromellose".

MYLAN RESPONSE: As requested, the change was made and is included in the enclosed final printed outsert.

FDA COMMENT 2.d: WARNINGS
i. First paragraph, second sentence: ".....NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES SHOULD BE....."

MYLAN RESPONSE: As requested, the change was made and is included in the enclosed final printed outsert.

FDA COMMENT 2.d: WARNINGS
ii. Sixth paragraph, last sentence: "....discontinuing nitrofurantoin monohydrate/macrocrystals; hemolysis....."

MYLAN RESPONSE: As requested, the revision was made and is included in the enclosed final printed outsert.

FDA COMMENT 2.e.i: PRECAUTIONS, Geriatric Use:
First sentence: ".....studies of nitrofurantoin monohydrate/macrocrystals capsules did not..."

MYLAN RESPONSE: As requested, the change was made and is included in the enclosed final printed outsert.

FDA COMMENT 2.eii: PRECAUTIONS, Geriatric Use:
Second sentence: ".....clinical experience has not identified....." [delete " [redacted]]

MYLAN RESPONSE: As requested, the words ' [redacted] were deleted and is included in the enclosed final printed outsert

FDA COMMENT 2.f: Delete the sentence " [redacted]

MYLAN RESPONSE: As requested, the above sentence, which appears at the end of outsert was deleted as contained in the enclosed final printed outsert

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/sp

Enclosure

Desk Copy: Ms. Ruby Wu
Division of Labeling and Program Support
Office of Generic Drugs

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 5, 2003

MINOR AMENDMENT
(CMC INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N / AM

RE: NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES, 100MG
ANDA 76-648
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 9, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the CMC comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated July 9, 2003 (provided in Attachment O). In response to the Agency's comments of July 9th, Mylan wishes to amend this application as follows:

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

FDA COMMENT 1: DMF's # [redacted] respectively, have been found inadequate. The DMF holders have been informed. Please notify in your response that the holders have responded to the deficiencies.

MYLAN RESPONSE: Mylan has been notified by the [redacted], that an amendment that addresses all deficiencies noted by the Agency for the [redacted] have been submitted to DMF's # [redacted] respectively. Copies of [redacted] letters to the Agency dated August 6, 2003, are provided in Attachment A for the convenience of the reviewer.

FDA COMMENT 2: Please revise the specifications for the Nitrofurantoin Macrocrystals to:

a. include limit for related [redacted] and

MYLAN RESPONSE: Per the Agency's request, the chromatographic purity specification for Nitrofurantoin, USP (Anhydrous Macrocrystals) was revised to include a specification for [redacted] at a limit of NMT [redacted] The revised drug substance specifications and Certificate of Analysis are provided in Attachment B.

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FDA COMMENT 2b: tighten the limits of residual solvents, [redacted]

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN RESPONSE: As requested, the residual solvent limit for [redacted] was tightened from "not more than [redacted] to "not more than [redacted]. The residual solvent limit for [redacted], was tightened from "not more than [redacted] to "not more than [redacted]. The revised drug substance specifications for Nitrofurantoin, USP (Anhydrous Macrocrystals) and Certificate of Analysis are provided in Attachment B.

FDA COMMENT 3: Please revise specifications for Nitrofurantoin Monohydrate to:

a. include limit for related [redacted] and

MYLAN RESPONSE: Per the Agency's request, the chromatographic purity specification for Nitrofurantoin, USP (Monohydrate) was revised to include a specification for [redacted], at a limit of NMT [redacted] The revised drug substance specifications and Certificate of Analysis are provided in Attachment C.

FDA COMMENT 3b: tighten the limit of residual solvent, and [redacted]

MYLAN RESPONSE: As requested, Mylan has tightened the residual solvent, [redacted], limit from "not more than [redacted] to "not more than [redacted]. The revised drug substance specifications for Nitrofurantoin, USP (Monohydrate) and Certificate of Analysis are provided in Attachment C.

FDA COMMENT 4: Please tighten or justify the limit for individual impurity specifications of "NMT [redacted]" for Nitrofurantoin Monohydrate and Nitrofurantoin Macrocrystals.

MYLAN RESPONSE: Mylan has tightened the individual impurity limit for the chromatographic purity specification from "NMT [redacted] to "NMT [redacted] for both the Nitrofurantoin, USP (Anhydrous Macrocrystals) and (Monohydrate) drug substances. The revised specifications for Nitrofurantoin, USP (Anhydrous Macrocrystals) and (Monohydrate) drug substances and the corresponding Certificates of Analysis are provided in Attachments B and C, respectively.

FDA COMMENT 5: Your particle size specifications for the drug substance Nitrofurantoin Macrocrystals are different than that of the manufacturer. Please explain.

MYLAN RESPONSE: [redacted]

provided in Attachment D.

Redacted 3

Page(s) of trade secret and /or confidential commercial information

FDA COMMENT 4: Please provide any additional long term stability data that may be available.

MYLAN RESPONSE: In response to the Agency's request, updated room temperature stability data through 12 months is provided in Attachment N for Nitrofurantoin Monohydrate/Macrocrystals Capsules, 100mg – Lot R1K1068.

FDA COMMENT 5: Please update all references to the current USP.

MYLAN RESPONSE: Any methods that are tested according to the USP for Nitrofurantoin, USP (Monohydrate), Nitrofurantoin, USP (Macrocrystals) and Nitrofurantoin Monohydrate/Macrocrystals Capsules, reference the current USP. In the event Nitrofurantoin Monohydrate/Macrocrystals Capsules become an official USP article, Mylan commits to revise the release specifications to reflect the required monograph testing (where applicable).

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn
Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 7, 2003

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

ORIG AMENDMENT
N/am

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES, 100MG
ANDA 76-648

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Minor Amendment submitted on September 5, 2003 which was in response to CMC comments pertaining to this application provided to Mylan on July 9, 2003. Reference is also made to a telephone conversation held today with Dr. Shing Liu, of your Office, regarding the In-Process [redacted] Specifications for the Nitrofurantoin Monohydrate Formulation included in our September 5, 2003 Amendment.

As discussed with Dr. Liu, Mylan has recently initiated the manufacture of [redacted] production size batches of Nitrofurantoin Monohydrate Formulation (Batches [redacted]. As indicated in Section XII, Page 4510 of the original ANDA, the proposed in-process specifications are further evaluated during the manufacture of the first [redacted] full scale production lots. Based on [redacted] data obtained from these recent production size batches of Nitrofurantoin Monohydrate Formulation, Mylan proposes to revise the tapped density specifications from [redacted]

The following table summarizes the [redacted] tapped density data obtained for all batches of Nitrofurantoin Monohydrate Formulation made to date.

Batch No.	Tapped Density
R1K1068 (exhibit batch)	[redacted]
1L3477	[redacted]
1L3478	[redacted]
1L3479	[redacted]

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The current and revised In-Process [redacted] Specifications for the Nitrofurantoin Monohydrate Formulation are provided in Attachments A and B, respectively. Data obtained for the [redacted] meet the established criteria for physical appearance, moisture, and [redacted], therefore, no other changes to the in process specifications are being proposed. Once this application is approved, the Agency will be notified of any proposed revisions to the established specifications in accordance with FDA regulations and guidance documents.

10-20

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

APPEARS THIS WAY
ON ORIGINAL

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 12, 2003

MINOR AMENDMENT
(CMC INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
MYLAN

RE: NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES, 100MG
ANDA 76-648
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 10, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the CMC comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated December 10, 2003 (provided in Attachment F). In response to the Agency's comments of December 10th, Mylan wishes to amend this application as follows:

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

FDA COMMENT 1: DMF's [redacted], Nitrofurantoin Macrocrystals and Nitrofurantoin Monohydrate respectively, have been found inadequate. The DMF holder has been informed. Please notify in your response that the holder has responded to the deficiencies.

MYLAN RESPONSE: Mylan has been notified by the [redacted] that an amendment that addresses all deficiencies noted by the Agency for the drug substances, Nitrofurantoin, USP (Anhydrous Macrocrystals) and Nitrofurantoin, USP (Monohydrate) have been submitted to DMF's [redacted] respectively. Copies of [redacted] letters to the Agency dated December 10, 2003, are provided in Attachment A for the convenience of the reviewer.

FDA COMMENT 2: Please justify the limit of moisture of NMT [redacted] or the Nitrofurantoin Macrocrystals tablet. We note that the manufacturing process for Nitrofurantoin Macrocrystals tablet is a [redacted], and the limit for moisture in the drug substance is NMT [redacted].

MYLAN RESPONSE: The in-process moisture limit of NMT [redacted] or the Nitrofurantoin Macrocrystals is derived from the calculated theoretical moisture of the ingredients as shown in the following example table.

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Department—Fax Numbers					
Accounting	(304) 285-6433	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Ingredient	Max %LOD*	mg/unit	% Moisture
Nitrofurantoin Macrocrystals	1.0	25.0	[redacted]
Microcrystalline Cellulose [redacted]	[redacted]	[redacted]	[redacted]
Lactose, Monohydrate [redacted]	[redacted]	[redacted]	[redacted]
Magnesium Stearate/SLS [redacted]	[redacted]	[redacted]	[redacted]
D&C Yellow #6 Lake	[redacted]	[redacted]	[redacted]
	TOTAL	**200.0**	[redacted]

*USP 26 / NF 21 Specification

Based on this data, Mylan wishes to retain the limit of NMT [redacted] for the Nitrofurantoin Macrocrystals [redacted]

FDA COMMENT 3: If the Nitrofurantoin Macrocrystals is shown to absorb moisture during manufacturing, please clarify the solid state (hydrate) form of Nitrofurantoin Macrocrystals in the Tablets.

MYLAN RESPONSE: In response to the Agency's comment, retain samples of Nitrofurantoin Macrocrystals portion obtained from the exhibit batch (Lot R1K1068) at various steps of the manufacturing process were tested for loss on drying. As seen in the table below, there is no evidence of moisture absorption during the course of manufacturing the Nitrofurantoin Macrocrystals part of the finished drug product.

Manufacturing Step at Which the Sample Was Taken	Average Moisture Value (%LOD)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

APPEARS THIS WAY
ON ORIGINAL

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

FDA COMMENT 1: Please provide any additional long term stability data that may be available.

MYLAN RESPONSE: In our minor amendment submitted on September 5, 2003, we provided 12 months room temperature stability data. No new stability data has been generated. However, we have enclosed updated stability data tables which reflect the revised dissolution limits proposed for the finished product (Attachment B).

FDA COMMENT 2: Bioequivalency deficiencies were communicated to you on October 31, 2003 and have not been responded. Please provide a response to the bioequivalency deficiencies.

MYLAN RESPONSE: Mylan has responded to the bioequivalency comments received from the Agency on October 31, 2003. A response to these comments was submitted as a Bioequivalence Amendment submitted this same date under separate cover. In accordance with our Bioequivalence Amendment, we have revised our finished product specifications and corresponding Certificate of Analysis, dissolution method (FP-NITMON-DS-M) and post-approval stability protocols (Attachments C, D and E, respectively).

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

3.1

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

February 12, 2004

BIOEQUIVALENCE AND TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

RE: NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS CAPSULES, 100MG
ANDA 76-648
RESPONSE TO AGENCY CORRESPONDENCE AND TELEPHONE CALL
RECEIVED FEBRUARY 4, 2004

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated February 4, 2004 (refer to Attachment E). Reference is also made to a telephone call received on February 4, 2004 from Ms. Wanda Pamphile, of your Office, in which she requested we provide revised documentation to the Division of Chemistry once a dissolution specification has been provided to us from the Division of Bioequivalence.

In response to the February 4th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted using the following method:

Medium:	0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume:	900 mL
Apparatus:	USP Apparatus 2 (Paddle) at 100 rpm
Sampling times:	1, 3, 7 and 14 hours

The specifications for your test product have been changed. The test product should meet the following specifications:

1 hour:	Between [redacted]
3 hours:	Between [redacted]
7 hours:	Between [redacted]
14 hours:	Not less than [redacted]

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

MYLAN RESPONSE: As requested, the following dissolution testing requirements for Nitrofurantoin Monohydrate/Macrocrystals Capsules, 100mg have been incorporated into Mylan's stability and quality control programs:

Medium:	0.01N HCl for 1 hour then changed to phosphate buffer, pH 7.5 thereafter
Volume:	900 mL
Apparatus:	USP Apparatus 2 (Paddle) at 100 rpm
Sampling times:	1, 3, 7 and 14 hours

The finished product specifications have been changed to meet the following specifications:

1 hour:	Between [redacted]
3 hours:	Between [redacted]
7 hours:	Between [redacted]
14 hours:	Not less than [redacted]

Revised finished product specifications and corresponding Certificate of Analysis, dissolution procedure (FP-NITMON-DS-M), and pre- and post-approval stability protocols are provided in Attachments A, B and C, respectively.

In addition, Mylan is including dissolution data on retain samples from our three month accelerated stability program as requested in the telephone call received on February 4, 2004 from Ms. Wanda Pamphile, of your Office (refer to Attachment D).

Mylan acknowledges that the bioequivalence comments provided in the February 4, 2004 communication are preliminary and that these comments may be revised after review of the entire application. It is also understood that the reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Ms. Wanda Pamphile (via facsimile and hard copy)