CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

16-620 / S-064

Trade Name: **Macrodantin**

Generic Name: **Nitrofurantoin macrocrystals**

Sponsor: **Proctor and Gamble Pharmaceuticals, Inc.**

Approval Date: **February 4, 2003**

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APPLICATION NUMBER:

16-620 / S-064

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 16-620/S-064

Procter & Gamble Pharmaceuticals, Inc.
Attention: Victoria Ireland
U.S. Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Ms. Ireland:

Please refer to your supplemental new drug application dated August 2, 2002, received August 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macrodantin® (nitrofurantoin macrocrystals) Capsules.

This supplemental new drug application provides for the addition of a **Geriatric Use** subsection in the **PRECAUTIONS** section in accordance with the "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling" Final Rule.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on August 2, 2002.

However, at the time of the next printing, please revise your FPL as follows:

1. In the first sentence of the **Geriatric Use** subsection, the word "nitrofurantoin" should be changed to "Macrodantin".

2. In the second sentence of the **Geriatric Use** subsection, the words "in the literature" should be deleted, since they are not included in the sentence under 21 CFR 201.57(f)(10)(ii)(A).

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Beth Duvall-Miller, Regulatory Health Project Manager, at (301) 827-2128.

Sincerely yours,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth
2/4/03 04:29:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

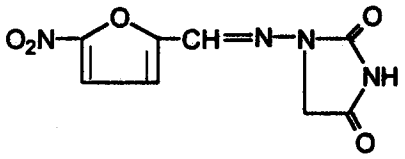
16-620 / S-064

LABELING

Macrodantin®
(nitrofurantoin macrocrystals)

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

DESCRIPTION: Macrodantin (nitrofurantoin macrocrystals) is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. **Macrodantin** is an antibacterial agent for specific urinary tract infections. It is available in 25 mg, 50 mg, and 100 mg capsules for oral administration.



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

Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD&C Yellow No. 6 and D&C Yellow No. 10.

CLINICAL PHARMACOLOGY: Macrodantin is a larger crystal form of **Furadantin®** (nitrofurantoin). The absorption of **Macrodantin** is slower and its excretion somewhat less when compared to **Furadantin**. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine, to which it may impart a brown color.

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

Unlike many drugs, the presence of food or agents delaying gastric emptying can increase the bioavailability of **Macrodantin**, presumably by allowing better dissolution in gastric juices.

Microbiology: 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 **Macrodantin**, has been shown to be active against most strains of the following bacteria both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**):

Gram-Positive Aerobes
Staphylococcus aureus
Enterococci (e.g., *Enterococcus faecalis*)

Gram-Negative Aerobes
Escherichia coli

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

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

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

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

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

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

Susceptibility Tests:
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	4-16
S. aureus ATCC 29213	8-32
E. faecalis ATCC 29212	4-16

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)
15-16	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	20-25
S. aureus ATCC 25923	18-22

INDICATIONS AND USAGE: Macrodantin is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli,* enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Macrodantin** and other antibacterial drugs, **Macrodantin** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by 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 **Macrodantin** are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with **Macrodantin**, other therapeutic agents with broader tissue distribution should be selected. In considering the use of **Macrodantin**, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.

Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38-42 weeks' gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.

Macrodantin is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

WARNINGS: ACUTE, SUBACUTE, OR CHRONIC PULMONARY REACTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH NITROFURANTOIN. IF THESE REACTIONS OCCUR, MACRODANTIN SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. REPORTS HAVE CITED PULMONARY REACTIONS AS A CONTRIBUTING CAUSE OF DEATH.

CHRONIC PULMONARY REACTIONS (DIFFUSE INTERSTITIAL PNEUMONITIS OR PULMONARY FIBROSIS, OR BOTH) CAN DEVELOP INSIDIOUSLY. THESE REACTIONS OCCUR RARELY AND GENERALLY IN PATIENTS RECEIVING THERAPY FOR SIX MONTHS OR LONGER. CLOSE MONITORING OF THE PULMONARY CONDITION OF PATIENTS RECEIVING LONG-TERM THERAPY IS WARRANTED AND REQUIRES THAT THE BENEFITS OF THERAPY BE WEIGHED AGAINST POTENTIAL RISKS (SEE RESPIRATORY REACTIONS).

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 **Macrodantin**; 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 **Macrodantin** with food to further enhance tolerance and improve drug absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms occur during therapy.

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

Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking **Macrodantin**.

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

General: Prescribing **Macrodantin** 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: Macrodantin is contraindicated in infants below the age of one month (see **CONTRAINDICATIONS**).

Geriatric Use: Clinical studies of **Macrodantin** 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 should be considered when prescribing **Macrodantin**. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria,

oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications (see **CONTRAINDICATIONS**). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS:
Respiratory:

CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR.

CHRONIC PULMONARY REACTIONS OCCUR GENERALLY IN PATIENTS WHO HAVE RECEIVED CONTINUOUS TREATMENT FOR SIX MONTHS OR LONGER. MALAISE, 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**).

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, nystagmus, dizziness, headache, and drowsiness also have been reported with the use of nitrofurantoin.

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported rarely. Bulging fontanels, as a sign of benign intracranial hypertension in infants, have been reported rarely.

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

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

Gastrointestinal: Nausea, emesis, and anorexia occur most often. Abdominal pain and diarrhea are less common gastrointestinal reactions. These dose-related reactions can be minimized by reduction of dosage. Sialadenitis and pancreatitis have been reported. There have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment (see **WARNINGS**).

Hematologic: Cyanosis secondary to methemoglobinemia has been reported rarely.

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

Laboratory Adverse Events: The following laboratory adverse events have been reported with the use of nitrofurantoin: increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, 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 **Macrodantin** have not resulted in any specific symptoms other than vomiting. Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug. It is dialyzable.

DOSAGE AND ADMINISTRATION: **Macrodantin** should be given with food to improve drug absorption and, in some patients, tolerance.

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

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

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

For long-term suppressive therapy in adults, a reduction of dosage to 50-100 mg at bedtime may be adequate. For long-term suppressive therapy in pediatric patients, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate. **SEE WARNINGS SECTION REGARDING RISKS ASSOCIATED WITH LONG-TERM THERAPY.**

HOW SUPPLIED: Macrodantin is available as follows:

25 mg opaque, white capsule imprinted with one black line encircling the capsule and coded "MACRODANTIN 25 mg" and "0149-0007."*

NDC 0149-0007-05 bottle of 100

50 mg opaque, yellow and white capsule imprinted with two black lines encircling the capsule and coded "MACRODANTIN 50 mg" and "0149-0008."*

NDC 0149-0008-05 bottle of 100
NDC 0149-0008-67 bottle of 1000

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

NDC 0149-0009-05 bottle of 100
NDC 0149-0009-67 bottle of 1000

*Capsule design, registered trademark of Procter & Gamble Pharmaceuticals.

Rx Only

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.

Procter & Gamble Pharmaceuticals
Cincinnati, OH 45202

REVISED June 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-064

MEDICAL REVIEW(S)

Clinical Review of Supplement

NDA: 16-620/S-064

Date of Submission: August 2, 2002

Date of Review: November 13, 2002

Applicant: Proctor & Gamble

Drug - Generic: Nitrofurantoin
Trade: Macrodantin® (nitrofurantoin macrocrystals) capsules
Class: Antibacterial

Route of Administration: Oral

Material Reviewed: One volume

Purpose of Submission

The applicant has filed this supplement in accordance with provisions found under 21 CFR 201.57, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs. The submission contains a revised package insert with the addition of a Geriatric Use subsection under PRECAUTIONS in accordance with statements found under sections 21 CFR 201.57(f)(10)(ii)(A) and 21 CFR 201.57(f)(10)(iii)(B).

In support of this revision, the applicant has included results from two controlled studies involving Macrobid and Macrodantin, results from a search of the scientific/medical literature, and the results of a review of the applicant's spontaneous safety database. The data from the clinical trials show that 57 of the 469 patients who received Macrobid and 64 of the 475 patients who received Macrodantin were ≥65 years of age.

Revisions to the Labeling

A Geriatric Use subsection has been added to the PRECAUTIONS section, along with the following statement:

> "**Geriatric Use:** Clinical studies of [redacted] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in the literature 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 Macrodantin. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications (see **CONTRAINDICATIONS**). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

Executive Summary

The applicant wishes to add a Geriatric Use subsection and statement to the PRECAUTIONS section as required by 21 CFR 201.57(f)(10). The statement includes two paragraphs taken from 21 CFR 201.57(f)(10)(ii)(A) and (iii)(B). The first paragraph states that clinical studies with nitrofurantoin did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects. The second paragraph refers to excretion of the drug by the kidney and the risk of toxic reactions in patients, such as the elderly, with impaired renal function. In addition, the applicant has added four sentences taken from other sections of the current labeling. The submission contained the results of two clinical trials which showed that 64 of 475 patients who received Macrodantin were 65 years or older. Also included were the results of a search of the medical literature and a search of the applicant's safety database. The latter search showed a higher proportion of pulmonary and hepatic adverse reactions in elderly patients. A review of the FDA AERS Datamart showed similar results. It is recommended that the supplement be approved with two minor modifications to the statement.

Data to support the addition.

Results from Controlled Studies of Nitrofurantoin (currently marketed as Macrodantin and Macrobid).

The following information was extracted from the submission.

A. Study 87051: A double-blind, multicenter study to compare the safety and efficacy of nitrofurantoin modified release capsules 100 mg BID for 7 days to Macrodantin® capsules 50 mg QID for 7 days in the treatment of urinary tract infections.

There were 224 subjects enrolled in this study who received Macrobid®, nitrofurantoin modified release capsules, and 223 subjects who received Macrodantin. Of the 224

subjects who received Macrobid, 32 (14.3%) subjects were ≥65 years of age. Of the 223 subjects who received Macrodantin, 34 (15.2%) subjects were ≥65 years of age.

Clinical Reviewer's Comment:

Macrobid consists of 25% macrocrystalline nitrofurantoin and 75% nitrofurantoin monohydrate, while Macrodantin is 100% nitrofurantoin macrocrystals.

There was no significant difference in the percentage of patients reporting adverse events between the two age groups (i.e., <65 years of age and ≥65 years of age) [Fischer's exact test]. In addition, there was no difference in the reporting incidence of individual COSTART terms between the two age groups. One subject in the Macrobid treatment group (<65 years of age) and one subject in the Macrodantin group (≥65 years of age) reported a serious adverse event. Moreover, there were no clinical meaningful differences in the mean change from baseline values for the laboratory data between the elderly and younger age groups or in the graphical plots showing the mean values of laboratory parameters over time.

There were an insufficient number of geriatric subjects enrolled in this study to make meaningful efficacy comparisons between the elderly and younger populations. However, an analysis of efficacy was performed on the limited number of elderly patients and there were no differences identified between the elderly and younger populations. The following table, showing these results, was extracted from the submission.

Table 1
Macrobid Study 87051
Bacteriological Response for Visit 3

Classification Visit 3	Macrobid					Macrodantin				
		<65 Years		≥65 Years			<65 Years		≥65 Years	
	N	n	(%)	n	(%)	N	n	(%)	n	(%)
Cure	76	60	(89.6)	16	(94.1)	85	66	(86.8)	19	(90.5)
Improvement	2	1	(1.5)	1	(5.9)	4	3	(3.9)	1	(4.8)
Failure	6	6	(9.0)	0	(0.0)	8	7	(9.2)	1	(4.8)
p-value	0.30					1.00				

N = total number of patients in treatment group and category
N (%) =number and percent of patients in treatment and age group and category
p-value is from the Fisher-Freeman-Halton exact test

Table 2
Macrobid Study 87051
Bacteriological Response for Visit 4

	Macrobid	Macrodantin

Classification Visit 4	N	<65 Years n	<65 Years (%)	≥65 Years n	≥65 Years (%)	N	<65 Years n	<65 Years (%)	≥65 Years n	≥65 Years (%)
Cure	63	51	(81.0)	12	(70.6)	67	52	(72.2)	15	(71.4)
Improvement	5	5	(7.9)	0	(0.0)	6	5	(6.9)	1	(4.8)
Failure	2	2	(3.2)	0	(0.0)	3	2	(2.8)	1	(4.8)
Relapse	10	5	(7.9)	5	(29.4)	17	13	(18.1)	4	(19.0)
p-value			0.10					0.96		
Re-infection	6	4	(6.3)	2	(11.8)	6	4	(5.6)	2	(9.5)
p-value			0.60					0.62		

N = total number of patients in treatment group and category
N (%) =number and percent of patients in treatment and age group and category
p-value is from the Fisher-Freeman-Halton exact test

Clinical Reviewer's Comments:

Of the 223 subjects enrolled in Study 87051 who received Macrodantin, 97 patients were microbiologically evaluable at visit 3 (presumed test of cure) and 89 patients were microbiologically evaluable at visit 4 (presumed follow-up visit). There were 21 elderly patients evaluated at both visits, while 76 adult patients <65 years old were evaluated at visit 3 and 72 adult patients were evaluated at the last visit. The elderly patients had a higher cure rate at visit 3 (90.5% vs 86.8%); however, at visit 4 the cure rate for this group dropped to 71.4% and the relapse rate was slightly higher than that of the adult patients <65 years old (19.0% vs 18.1%).

B. Study 87052: A double-blind, multicenter study to compare the safety and efficacy of nitrofurantoin modified release capsules 100 mg BID for 7 days to Macrodantin® capsules 50 mg QID for 7 days in the treatment of urinary tract infections.

There were 245 subjects enrolled in this study who received Macrobid®, nitrofurantoin modified release capsules, and 252 subjects who received Macrodantin. Of the 245 subjects who received Macrobid, 25 (10.2%) subjects were ≥65 years of age. Of the 252 subjects who received Macrodantin, 30 (11.9%) subjects were ≥65 years of age.

There was no significant difference in the percentage of patients reporting adverse events between the two age groups (i.e., <65 years of age and ≥65 years of age)[Fischer's exact test]. In addition, there was no difference in the reporting incidence of individual COSTART terms between the two age groups. One subject in the Macrobid treatment group (<65 years of age) and two subjects in the Macrodantin group (one subject in each; <65 years of age and ≥65 years of age) reported a serious adverse event. Moreover, there were no clinically meaningful differences in the mean change from baseline values for the laboratory data between the elderly and younger age groups or in the graphical plots showing the mean values of laboratory parameters over time.

There were an insufficient number of geriatric subjects enrolled in this study to make meaningful efficacy comparisons between the elderly and younger populations. However, an analysis of efficacy was performed on the limited number of elderly patients and there were no differences identified between the elderly and younger populations. The following tables show the results of study 87052 and the combined results of studies 87051 and 87052.

Table 3
Macrobid Study 87052
Bacteriological Response for Visit 3

Classification Visit 3	Macrobid					Macrodantin				
		<65 Years		≥65 Years			<65 Years		≥65 Years	
	N	n	(%)	n	(%)	N	n	(%)	n	(%)
Cure	97	86	(86.9)	11	(84.6)	88	76	(80.9)	12	(92.3)
Improvement	1	1	(1.0)	0	(0.0)	7	7	(7.4)	0	(0.0)
Failure	14	12	(12.1)	2	(15.4)	12	11	(11.7)	1	(7.7)
p-value	0.71					0.85				

N = total number of patients in treatment group and category
N (%) =number and percent of patients in treatment and age group and category
p-value is from the Fisher-Freeman-Halton exact test

Table 4 Macrobid Study 87052 Bacteriological Response for Visit 4										
	Macrobid					Macrodantin				
Classification		<65 Years		≥65 Years			<65 Years		≥65 Years	
Visit 4	N	n	(%)	n	(%)	N	n	(%)	n	(%)
Cure	79	70	(78.7)	9	(75.0)	74	65	(75.6)	9	(75.0)
Improvement	6	5	(5.6)	1	(8.3)	7	7	(8.1)	0	(0.0)
Failure	4	3	(3.4)	1	(8.3)	5	5	(5.8)	0	(0.0)
Relapse	12	11	(12.4)	1	(8.3)	12	9	(10.5)	3	(25.0)
p-value	0.62					0.44				
Re-infection	6	4	(4.5)	2	(16.7)	2	2	(2.3)	0	(0.0)
p-value	0.15					1.00				
N = total number of patients in treatment group and category N (%) =number and percent of patients in treatment and age group and category p-value is from the Fisher-Freeman-Halton exact test										

Clinical Reviewer's Comments:

Of the 252 subjects enrolled in Study 87052 who received Macrodantin, 107 patients were microbiologically evaluable at visit 3 and 98 patients were microbiologically evaluable at visit 4. There were 13 elderly patients evaluated at visit 3 and 12 at visit 4. There were 94 adult patients <65 years old evaluated at visit 3 and 86 evaluated at the last visit. At visit 3, the elderly patient population had a higher cure rate, 92.3% vs 80.9%; however, at the last visit the cure rates were equal, 75.0% for the elderly group compared to 75.6% for the adults <65 years old. The relapse rate was higher for the elderly population, 25.0% vs 10.5%, while the re-infection rate for the adult patients <65 years old exceeded that of the elderly group, 2.3% vs 0.0%.

Table 5 Combined Macrobid Studies 87051 and 87052 Bacteriological Response for Visit 3										
	Macrobid					Macrodantin				
Classification		<65 Years		≥65 Years			<65 Years		≥65 Years	
Visit 3	N	n	(%)	n	(%)	N	n	(%)	n	(%)
Cure	173	146	(88.0)	27	(90.0)	173	142	(83.5)	31	(91.2)
Improvement	3	2	(1.2)	1	(3.3)	11	10	(5.9)	1	(2.9)
Failure	20	18	(10.8)	2	(6.7)	20	18	(10.6)	2	(5.9)
p-value	0.51					0.66				
N = total number of patients in treatment group and category N (%) =number and percent of patients in treatment and age group and category p-value is from the Fisher-Freeman-Halton exact test										

Table 6
Combined Macrobid Studies 87051 and 87052
Bacteriological Response for Visit 4

Classification Visit 4	Macrobid					Macrodantin				
		<65 Years		≥65 Years			<65 Years		≥65 Years	
	N	n	(%)	n	(%)	N	n	(%)	n	(%)
Cure	142	121	(80.0)	21	(72.4)	141	117	(74.0)	24	(72.7)
Improvement	11	10	(6.6)	1	(3.5)	13	12	(7.6)	1	(3.0)
Failure	6	5	(3.3)	1	(3.5)	8	7	(4.4)	1	(3.0)
Relapse	22	16	(10.5)	6	(20.7)	29	22	(13.9)	7	(21.2)
p-value	0.0.45					0.64				
Re-infection	12	8	(5.3)	4	(13.8)	8	6	(3.8)	2	(6.1)
p-value	0.10					0.63				

N = total number of patients in treatment group and category
N (%) =number and percent of patients in treatment and age group and category
p-value is from the Fisher-Freeman-Halton exact test

Clinical Reviewer's Comments:

Of the 475 patients enrolled in Studies 87051 and 87052 who received Macrodantin, 64 (13.5%) were 65 years of age or older. Among the 64 elderly patients, only 33 were microbiologically evaluable at the fourth visit. Therefore, the data support the applicant's statement that the clinical studies did not contain "sufficient numbers of subjects aged 65 and over", i.e., at least 100 subjects according to the FDA guideline and Federal Register Notice [62FR45313].

In the Geriatric Use statement found under 21 CFR 201.57(f)(10)(ii)(A), the applicant has inserted [redacted] for the name of the drug, rather than the trade name Macrodantin have different formulations, data from the two drug products should not be combined. Thus, the correct name for this product in the sentence should be Macrodantin. The applicant has already submitted a separate supplement to NDA 20-064 for Macrobid for the same purpose.

Results of a Literature Review of Nitrofurantoin Products (currently marketed as Macrodantin and Macrobid).

The applicant searched the following databases for clinical trials of nitrofurantoin (i.e., Medline, EmBase, Scisearch, BIOSIS, and Chemical Abstracts using the following search terms to describe the elderly population (i.e., elder, geriat, geront, or nursing home). Twelve literature citations were retrieved. The applicant included the following summary of a review of the references. None of the articles were relevant. With regard to efficacy, no study approached having enough elderly subjects to make a meaningful comparison of outcomes between the elderly and the younger population. With regard to safety, none of the studies contained data indicating adverse events differed between

the elderly and younger subjects. Depending on the study, adverse reactions were either not reported or the reported adverse events were not broken out by elderly versus younger subjects precluding direct comparisons between the two age groups.

Clinical Reviewer's Comments:

A review of the literature references was performed, agreeing with the applicant's assessment.

Results of a Review of the Spontaneous Safety Database for Nitrofurantoin Products (currently marketed as Macrodantin and Macrobid).

The applicant included a very detailed, 48 page report which describes the results of a search of the adverse event database for nitrofurantoin and a possible method for evaluating those results, based on "reporting ratios". This approach assumes that elderly and adult patients report the same types of adverse events at the same rate, and that a difference between populations in the reporting rate reflects a difference between populations in the event occurrence. The objective of the search was to compare the reported adverse event experiences of adult patients with those of elderly patients. A search of the database (n=7448 cases) was conducted and the reports were tabulated according to age group as follows: pediatric (≤16 years old, n=282); adult (17-64 years old, n=2105); elderly (≥65 years old, n=1215); and unknown (n=3846).

Population ratios (number of reports in the elderly population versus the number of reports in the adult population) were then determined for the MedDRA System Organ Classes (SOCs) and the Preferred Terms (PTs). For example, the comparative ratio for the populations of interest (elderly versus adult) for the nitrofurantoin products was 1215÷2105 = 0.58. When the elderly/adult ratio for a particular SOC or PT exceeded the comparative ratio, a statistical analysis of the difference between populations was performed using a 1-tailed Z-test, α=0.05, where a test statistic value of ≥1.645 indicated that the reporting rate in the elderly population was significantly greater than that in the adult population. The following tables, extracted from the report, show the results of this analysis of adverse events according to SOC and Preferred Terms.

Table 7 Population Characteristics, Elderly versus Adult Populations				
	Elderly Population N = 1215		Adult Population <65 years old N = 2105	
Average age (yrs ± std dev)	74.6 ± 6.7		44.1 ± 13.2	
Gender	n	%	n	%
Female	843	69.4	1748	83.0
Male	329	27.1	311	14.8
Unknown/Blank	43	3.5	46	2.2
Duration of Therapy	n	%	n	%
≤15 days	466	38.4	975	46.3
>15 days to ≤60 days	80	6.6	123	5.8
>60 days to ≤180 days	67	5.5	67	3.2
>180 days	209	17.2	176	8.4
Unknown	393	32.3	176	36.3
Intercurrent diagnoses Number (average)	2369	(1.9/patient)	2699	(1.3/patient)
Concomitant medications Number (mean)	2975	(2.4/patient)	3274	(1.6/patient)

Table 7 shows the population demographics, duration of therapy, and medical history characteristics of the two populations. The following points can be made. More females than males experienced adverse events among both populations, which is to be expected since the drug is prescribed for urinary tract infections, which generally occur more often among women. The elderly population received the drug for longer periods of time, had more diagnoses associated with their therapies, and received more concomitant drugs than the adult population.

Clinical Reviewer's Comments:

The data from the table support the applicant's statement to the Geriatric Use subsection that possible differences in rates between the two populations for certain adverse reactions, e.g., pulmonary, hepatic reactions, may be "related to the higher proportion of elderly patients receiving long-term nitrofurantoin therapy." For example, 17.2% of the elderly patients received therapy for more than 180 days compared to 8.4% of the adult patients.

Table 8 Number and Percentage of Reports, by Primary SOC and Population						
	Elderly Population N = 1215		Adult Population <65 years old N = 2105		ratio	z
System Organ Class	n	%	n	%		
General/administration site	480	39.5	866	41.1	0.55	
Respiratory/thoracic	**437**	**36.0**	**554**	**26.3**	**0.79**	**5.848**
Gastrointestinal	280	23.0	589	28.0	0.48	
Skin/subcutaneous tissue	261	21.5	582	27.6	0.45	
Nervous system	247	20.3	519	24.7	0.48	
Infections and infestations	**233**	**19.2**	**280**	**13.3**	**0.83**	**4.487**
Blood/lymphatic system	131	10.8	205	9.7	0.52	
Hepato-biliary	128	10.5	204	9.7	0.63	0.680
Cardiac	99	8.1	158	7.5	0.63	0.557
Musculoskeletal	85	7.0	261	12.4	0.33	
Metabolism/nutrition	**84**	**6.9**	**92**	**4.4**	**0.91**	**3.018**
Psychiatric	53	4.4	76	3.6	0.7	1.054
Renal/urinary	52	4.3	74	3.5	0.7	1.068
Vascular	45	3.7	90	4.3	0.5	
Immune	42	3.5	103	4.9	0.41	
Eye	25	2.1	49	2.3	0.51	
Ear/labyrinth	14	1.2	27	1.3	0.52	
Injury and poisoning	13	1.1	23	1.1	0.56	
Neoplasms benign/malignant	9	0.7	9	0.4	1.00	0.929
Reproductive/breast	8	0.7	21	1.0	0.38	
Congenital/familial/genetic	4	0.3	31	1.5	0.13	
Endocrine	2	0.2	6	0.3	0.33	
Pregnancy/puerperium/ Perinatal	0	0	25	1.2	0	

In Table 8, ratios for 8 of 23 SOCs exceeded the comparative ratio for the elderly versus adult population (0.58); the elderly reporting rate was statistically greater than the adult reporting rate for 3 SOCs, respiratory/thoracic, infections and infestations, and metabolism/nutrition. The most frequently reported SOCs (reported by greater than 10% of the elderly population) were General disorders and administration site conditions, respiratory/thoracic, gastrointestinal, skin & subcutaneous tissue, nervous system disorders, infections and infestations, blood and lymphatic system disorders, and hepato-biliary disorders.

Clinical Reviewer's Comments:

The data support the applicant's statement regarding possible differences between the two populations with respect to pulmonary adverse events. The data concerning possible hepato-biliary differences are not very strong, i.e., the Z number = 0.68.

Table 9
Preferred Terms Reported by 1% or More of the Elderly Population

	Elderly Population N = 1215		Adult Population <65 years old N = 2105		ratio	z
Preferred Term	n	%	n	%		
Dyspnea	**271**	**22.3**	**342**	**16.2**	**0.79**	**4.314**
Pyrexia	235	19.3	457	21.7	0.51	
Pneumonia NOS	**183**	**15.1**	**226**	**10.7**	**0.81**	**3.664**
Cough	**166**	**13.7**	**218**	**10.4**	**0.76**	**2.804**
Nausea	144	11.9	310	14.7	0.46	
Pulmonary fibrosis	**116**	**9.5**	**59**	**2.8**	**1.97**	**8.223**
Dermatitis NOS	115	9.5	189	9.0	0.61	0.418
Peripheral neuropathy NEC	75	6.2	103	4.9	0.73	1.517
Death NOS	**70**	**5.8**	**29**	**1.4**	**2.41**	**7.060**
Malaise	65	5.3	118	5.6	0.55	
Rigors	63	5.2	117	5.6	0.54	
Vomiting	61	5.0	173	8.2	0.35	
Chest pain NEC	57	4.7	137	6.5	0.42	
Paresthesia	56	4.6	134	6.4	0.42	
Lung disorder NOS	**53**	**4.4**	**46**	**2.2**	**1.15**	**3.477**
Jaundice NOS	51	4.2	93	4.4	0.55	
Hepatitis NOS	49	4.0	90	4.3	0.54	
Anorexia	**48**	**4.0**	**55**	**2.6**	**0.87**	**2.141**
Asthenia	47	3.9	81	3.8	0.58	0.050
Pruritus NOS	45	3.7	144	6.8	0.31	
Eosinophilia (Exc. Pulmonary)	44	3.6	77	3.7	0.57	
Pain NOS	44	3.6	94	4.5	0.47	
Liver function tests NOS abn	43	3.5	75	3.6	0.57	
Fatigue	42	3.5	75	3.6	0.56	
Weakness	**41**	**3.4**	**47**	**2.2**	**0.87**	**1.982**
Headache NOS	38	3.1	146	6.9	0.26	
Pneumonitis	**36**	**3.0**	**19**	**0.9**	**1.89**	**4.379**
Dizziness (exc. Vertigo)	34	2.8	74	3.5	0.46	
Urticaria NOS	31	2.6	125	5.9	0.25	
Abdominal pain NOS	30	2.5	63	3.0	0.48	
Weight decreased	**30**	**2.5**	**20**	**1.0**	**1.50**	**3.284**
Confusion	**29**	**2.4**	**14**	**0.7**	**2.07**	**4.013**
Hypoxia	**29**	**2.4**	**22**	**1.0**	**1.32**	**3.055**

Continued on next page

Table 9 Continued Preferred Terms Reported by 1% or More of the Elderly Population						
	Elderly Population N = 1215		Adult Population <65 years old N = 2105		ratio	z
Preferred Term	n	%	n	%		
Diarrhea NOS	28	2.3	51	2.4	0.55	
Aspartate aminotransferase inc	28	2.3	49	2.3	0.57	
Arthralgia	28	2.3	90	4.3	0.31	
Hypersensitivity NOS	26	2.1	72	3.4	0.36	
Hypoesthesia	26	2.1	55	2.6	0.47	
Pleural effusion	26	2.1	33	1.6	0.79	0.909
Rash maculo-papular	26	2.1	70	3.3	0.37	
Myalgia	21	1.7	92	4.4	0.23	
Alanine aminotransferase inc	20	1.6	54	2.6	0.37	
Hyperbilirubinemia	19	1.6	37	1.8	0.51	
Antinuclear factor positive	18	1.5	23	1.1	0.78	0.857
Sweating increased	18	1.5	42	2.0	0.43	
Leukopenia NOS	17	1.4	30	1.4	0.57	
Somnolence	17	1.4	21	1.0	0.81	0.892
Thrombocytopenia	16	1.3	18	0.9	0.89	0.937
Leukocytosis NOS	16	1.3	18	0.9	0.80	0.937
Blood Alk phosphatase NOS inc	16	1.3	29	1.4	0.55	
Wheezing	16	1.3	21	1.0	0.76	0.626
Cyanosis NOS	15	1.2	19	0.9	0.79	0.657
Pulmonary edema NOS	15	1.2	23	1.1	0.65	0.093
Red blood cell sed rate inc	**15**	**1.2**	**12**	**0.6**	**1.25**	**1.667**
Lung infiltration NOS	15	1.2	16	0.8	0.94	0.988
Hypotension NOS	15	1.2	28	1.3	0.54	
Asthma NOS	13	1.1	25	1.2	0.52	
Petechiae	**13**	**1.1**	**10**	**0.5**	**1.30**	**1.784**
Abdominal pain upper	12	1.0	27	1.3	0.44	
Dry mouth	12	1.0	10	0.5	1.20	1.450
Hepatic cirrhosis NOS	**12**	**1.0**	**9**	**0.4**	**1.33**	**1.928**
Hepatic necrosis	**12**	**1.0**	**9**	**0.4**	**1.33**	**1.928**
Back pain	12	1.0	47	2.2	0.26	

In Table 9, the most frequently reported MedDRA preferred terms for ≥1% of the elderly population are listed in decreasing frequency in the elderly population. Of the 63 preferred terms reported most frequently in the elderly population, the ratios for 34 were less than the comparative ratio (i.e., elderly patients reporting adverse events did not report these terms more frequently than adult patients reporting adverse events). Of the remaining 29 preferred terms with ratios exceeding the comparative ratio (0.58), 16 were reported statistically more frequently in the elderly population than in adults.

Table 10 Summary of Deaths by Associated Body System and Patient Population				
	Elderly Population N = 85		Adult Population <65 years old N = 44	
Body System	n	%	n	%
Respiratory	37	43.5	12	27.3
Hepato-biliary	22	25.9	10	22.7
Cardiovascular	9	10.6	5	11.4
Hematologic	6	7.1	10	22.7
Allergic/Hypersens.	6	7.1	5	11.4
Digestive	3	3.5	2	4.5
Renal	2	2.3	0	0

Clinical Reviewer's Comments:

The data from the tables support the applicant's statement regarding possible differences between the two populations with respect to pulmonary adverse events (e.g., pneumonia NOS and pulmonary fibrosis) and hepatic events (e.g., hepatic cirrhosis NOS and hepatic necrosis). The number of deaths among the elderly support the applicant's inclusion of the words "including fatalities" to the sentences concerning pulmonary reactions and hepatic reactions in the geriatric use statement.

The applicant's method in analyzing the adverse event data using a "comparative ratio" approach was discussed with Dr. Thamban Valappil, HFD-520 Bio-statistician. He stated that the method has several statistical assumptions which may not be correct. The procedure assumes the following: a normal distribution of events occurs, assumes that each event occurrence or rate is the same for both populations, and it assumes that the occurrence of each adverse event is independent of the other events. All or none of the conditions may be true. Also, the mixing of serious events with mild or moderate events is not appropriate.

Nevertheless, the results obtained using "comparative ratios" to determine possible differences between populations based on age is an interesting approach. The results do support the applicant's statements regarding a possible "higher proportion of pulmonary reactions and severe hepatic reactions, including fatalities" in elderly patients. Additional support is found in the WARNINGS section of the current labeling. A large case, bolded paragraph warns of the possibility of serious pulmonary reactions in patients treated with nitrofurantoin. The second paragraph in that section warns of hepatic reactions that occur rarely.

Search of the FDA's AERS Datamart.

The AERS Datamart was searched for all MedWatch reports of adverse events associated with nitrofurantoin therapy that have been reported to the agency. Macrobid was selected as the Trade Name, nitrofurantoin as the ingredient name, and all reactions was chosen as the reaction type; the age groups were varied. The following table shows the results of that search according to specific age groups.

Table 11. Adverse events associated with nitrofurantoin therapy according to age groups.

Age Group Selected	Number of Cases Retrieved
All age categories – 7 groups (neonate – unknown)	4307
Adult (17 yrs - <65 yrs)	1573
Elderly – 65^{+}yrs	927
Age Unknown	1641

Clinical Reviewer's Comments:

The total number of MedWatch reports in the AERS database (n=4307) is considerably less than the number of reports in the applicant's database (n=7448). However, the comparative ratio (0.589) of the number of reports for the elderly (n=927) compared to the number of reports for adults (n=1573) was very similar to the ratio derived by the applicant (0.577).

Since the applicant observed a possible difference between elderly patients and younger patients in the number of reports submitted for respiratory events (e.g., pneumonia, lung disorder, etc.) and hepatic events (e.g., hepatic cirrhosis, hepatic necrosis), those adverse events were searched, along with death. The results for each age group are shown in the following table.

Table 12. Specific adverse events associated with nitrofurantoin therapy according to age groups.

Adverse Event	All Age Groups N = 4307	Adults Only <65 years old N = 1573	Elderly Only N = 927	Unknown Only N = 1641
Pneumonia NOS	325 (7.5%)	101 (6.4%)	135 (14.6%)	87 (5.3%)
Pulmonary fibrosis	207 (4.8%)	38 (2.4%)	88 (9.5%)	80 (4.9%)
Lung disorder	406 (9.4%)	90 (5.7%)	133 (14.3%)	180 (11.0%)
Pneumonitis	14 (0.32%)	5 (0.32%)	9 (0.97%)	0 (0.0%)
Hepatic cirrhosis NOS	25 (0.58%)	6 (0.38%)	11 (1.2%)	8 (0.49%)
Hepatic necrosis	29 (0.67%)	13 (0.82%)	6 (0.64%)	10 (0.61%)
Jaundice NOS	116 (2.7%)	45 (2.8%)	32 (3.4%)	35 (2.1%)
Hepatitis NOS	152 (3.5%)	66 (4.2%)	39 (4.2%)	43 (2.6%)
Death NOS	12 (0.28%)	3 (0.19%)	2 (0.21%)	7 (0.42%)

Clinical Reviewer's Comments:

The results of the search for these adverse events support the applicant's statement that elderly patients had a higher rate of pulmonary adverse events than adult patients. For the hepatic events, the results are similar for both populations, except for hepatic cirrhosis, where the elderly population had a higher rate. The death rate was similar for both groups.

Recommendation

It is recommended that the supplement be approved with the following modifications to the Geriatric Use Statement:

Paragraph 1

1. In the first sentence, the word ' [redacted] ould be changed to "Macrodantin".
2. In the second sentence, the words ' [redacted]
3. The remaining sentences in the paragraph are acceptable, as supported by the data in the submission and by their presence in the current labeling under WARNINGS.

Paragraph 2

There are no recommended changes to this paragraph. The statements are supported by the data in the submission and by their presence in the current labeling under CONTRAINDICATIONS.

The revised statement should read as follows:

"**Geriatric Use:** Clinical studies of Macrodantin 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 Macrodantin. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications (see **CONTRAINDICATIONS**). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

James Blank, Ph.D.

David Ross, M.D., Ph.D.

cc:
Orig. NDA
HFD-520
HFD-520/MO/DRoss
ClinRev/JBlank
Micro/ASheldon
CSO/RPeat
Pharm/ROsterberg
Chem/DKatague
Word/16-620.064;11-14-02;12-6-02

Concurrence Only:
HFD520/DivDir/JSoreth
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/s/

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