# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

*APPLICATION NUMBER:*

# 16-620 / S-065

**Trade Name:** Macrodantin

**Generic Name:** Nitrofurantoin macrocrystals

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

**Approval Date:** March 29, 2004

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 16-620 / S-065

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 16-620 / S-065

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 16-620/S-065

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

Dear Ms. Ireland:

Please refer to your supplemental new drug application dated August 21, 2003, received August 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macrodantin® (nitrofurantoin macrocrystals) Capsules. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

This supplemental application, submitted as a "Supplement - Changes Being Effected in 0 days" supplement, proposes the following change to be in compliance with the systemic antibacterial drug products labeling regulations as found in 21 CFR 201.24.

We have 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 22, 2003.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, 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 LT Raquel Peat, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

*{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

Enclosure: Labeling

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 16-620 / S-065

# LABELING

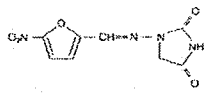
# Macrodantin®

95087757

(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

**Macrodantin** (nitrofurantoin macrocrystals)

**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, mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female B6C3F, 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

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.

**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.



**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.

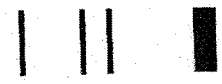


**Procter & Gamble Pharmaceuticals**
Cincinnati, OH 45202

REVISED June 2003


**Macrodantin®**
(nitrofurantoin macrocrystals)

9508757



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/s/
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Janice Soreth
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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 16-620 / S-065

# MEDICAL REVIEW(S)

# Medical Officer's Review of Labeling Supplement

**1.0 Identification:** NDA 16-620/SLR-065

**1.1 Applicant:** Proctor & Gamble Pharmaceuticals, Inc.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Contact Person: Victoria Ireland
Regulatory Affairs Manager

**1.2 Submission/Review Dates:**

Date of submission: August 21, 2003
Date assigned to MO: March 22, 2004
Date of review completion: March 22, 2004

**1.3 Drug identification:**

Generic Drug Name: Nitrofurantoin macrocrystals
Trade Name: Macrodantin®(nitrofurantoin macrocrystals) capsules
Dosage Form, Strengths, and Route of Administration: 25, 50, and 100 mg capsules for oral administration

Category: Nitrofuran class of antibacterial agent

**2.0 Purpose of Supplement**

This *Changes Being Effected* (CBE) supplement is submitted to add the labeling statements for systemic antibacterial drug products for Macrodantin, in accordance with 21 CFR §201.24. In addition, the changes requested by the Division in the February 4, 2003 approval letter for the Geriatric Use-CBE supplement are included in the text of the Geriatric Use subsection of the package insert for Macrodantin®.

## 3.0 Material submitted and reviewed:

The submission consisted of one volume for the labeling supplement for Macrodantin®. The volume consisted of the following materials:

- Cover letter, dated August 21, 2003;
- Application form (356h);
- Establishment Information;
- User fee cover sheet (Form 3397);
- Revised labeling for Macrodantin®;
- Final Printed Labeling for Macrodantin®

## 4.0 Review of proposed statements in selected sections of the package insert for Macrodantin®

The following revisions (underlined text) for the label of Macrodantin were added by the applicant:

A. At the beginning of the label under the product name the following statement has been added, which reads as follows:

"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."

***MO Comment***: *The above proposed statement for the labeling of Minocin regarding the development of drug-resistant bacteria is in accordance with 21 CFR § 201.24 (a). This revision is acceptable.*

B. In the "**INDICATIONS AND USAGE**" section, the following statements have been added as the third paragraph under this section:

"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."

***MO Comment**: The above proposed statements for the labeling of Macrodantin regarding the development of drug-resistant bacteria are in accordance with 21 CFR §201.24(b). This revision is acceptable.*

C. In the **"PRECAUTIONS"** section, the following statements were added under the "**Information for Patients**" subsection as the fourth paragraph:

"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."

- The following text was added under the "**General**" subsection:

"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."

***MO Comment**: The above proposed statements for the labeling of Macrodantin regarding the development of drug-resistant bacteria are in accordance with 21 CFR § 201.24 (c) and (d). These revisions are acceptable.*

D. In the "**Geriatric Use**" subsection, the applicant made the following revisions:

- In the first sentence of the **Geriatric Use** subsection, the word "nitrofuratoin" has been changed to "Macrodantin." The word "**Macrodantin**" is in bold letters.

- In the second sentence of the **Geriatric Use** subsection, the words "in the literature" have been deleted. The revised statements will now read as follows: (Note: The reviewer underlined the revision for emphasis.)

"**Geriatric Use:** Clinical studies of ~~nitrofurantoin~~ **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 ~~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 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 **CONTRAINDICATIIONS**). 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."

***MO Comment:*** *The above changes were requested by the Division in the February 4, 2003 approval letter for the Geriatric Use-CBE supplement for Macrodantin. These revisions are acceptable. The bold letters for the word "**Macrodantin**" is also acceptable.*

## 5.0 Conclusion and Recommendation

It is recommended that the labeling supplement for NDA 16-620/SLR-065 be approved.

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/s/
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