CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

16-620 / S-017

Trade Name: Macrodantin

Generic Name: (nitrofurantoin macrocrystals)

Sponsor: Norwich Pharmacal Company

Approval Date: July 21, 1976

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-017

APPROVAL LETTER

NDA 16-620/S-017

JUL 21 1976

Norwich Pharmacal Company
Attention: Alexander B. Neill, Ph.D.
Norwich, New York 13815

Gentlemen:

Reference is made to your supplemental new drug application of March 17, 1976, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macrodantin (nitrofurantoin macrocrystals) Capsules, 25, 50 and 100 mg.

We also acknowledge receipt of your additional communications dated June 16, 1976, and July 9, 1976, amending the supplement.

The supplemental application provides for a change of manufacturing facility, transfer of ownership of this NDA to Eaton Laboratories, Inc., Manati, Puerto Rico, an alternate manufacturing site and labeling changes reflecting the new facility.

We have completed the review of this supplemental application and it is approved. Our letter of April 11, 1968, detailed the conditions relating to the approval of this application.

Sincerely yours,

Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Bureau of Drugs

cc: NYK-DO
Orig NDA
HFD-140
HFD-140/CSO
HFD-140/HCZell/7/13/76/jmm/7/19/76 HCZ 7/19/76
R/D init. by: ARCasela/7/14/76 ARC 7/20/76

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-017

APPROVED LABELING

Labeling: Orig

NDA No: 16-620 Rec'd 6-10-76

Reviewed By: H.C. Will 7/14/76

42-15-31

MACRODANTIN®

(nitrofurantoin macrocrystals)

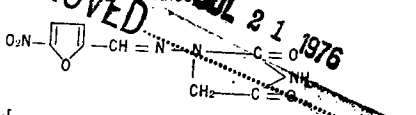
CAPSULES

Eaton Laboratories

7103

APPROVED JUL 21 1976

DESCRIPTION: Macrodantin (nitrofurantoin macrocrystals) is a synthetic chemical of controlled crystal size. It is a stable, yellow crystalline compound. It is supplied in 25 mg, 50 mg and 100 mg capsules.



1-[(5-NITROFURFURYLIDENE)AMINO]HYDANTOIN

ACTIONS: Macrodantin (nitrofurantoin macrocrystals) is a larger crystal form of Furadantin (nitrofurantoin). The absorption of Macrodantin is slower and the excretion of Macrodantin is somewhat less, when the two are compared. The reduced incidence of gastrointestinal intolerance with Macrodantin is probably due to delayed and decreased absorption; this, however, does not significantly reduce clinical effectiveness.

A number of patients who cannot tolerate Furadantin tablets are able to take Macrodantin capsules without nausea.

Macrodantin is an antibacterial agent for specific urinary tract infections. It is bacteriostatic in low concentrations (1:100,000 to 1:200,000) and in vitro is considered to be bactericidal in higher concentrations. Its presumed mode of action is based upon its interference with several bacterial enzyme systems. Bacteria develop only a limited resistance to furan derivatives.

Average urinary drug recoveries in 0-24 hours following a therapeutic dose regimen (100 mg qid for 7 days) on day 1 and day 7 were reported to be 37.9 and 35% respectively for this dosage form.

Nitrofurantoin is highly soluble in urine, to which it may impart a brown color.

INDICATIONS: Macrodantin is indicated for the treatment of pyelonephritis, pyelitis, and cystitis when due to susceptible E. coli, enterococci, S. aureus (it is not indicated for the treatment of associated renal cortical or perinephric abscesses), and certain strains of Klebsiella-Aerobacter, Proteus, and Pseudomonas.

In vitro susceptibility testing (disk or dilution techniques) may not be helpful in predicting patient response where the latter are the infecting organisms. This is probably related to marginal susceptibility of these organisms and variability in urine (and presumably renal medullary) levels of the drug achieved in various patients.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients at term as well as in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems (glutathione instability).

The drug is contraindicated in those patients with known hypersensitivity to Macrodantin (nitrofurantoin macrocrystals).

WARNINGS: Cases of hemolytic anemia of the primaquine sensitivity type have been induced by Macrodantin. The 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 Negroes and a small percent of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn.

Pseudomonas is the organism most commonly implicated in superinfections in patients treated with Macrodantin.

USAGE IN PREGNANCY: The safety of Macrodantin during pregnancy and lactation has not been established. It should not be used in women of childbearing potential unless the expected benefits outweigh the possible hazards.

PRECAUTIONS: Peripheral neuropathy may occur with Macrodantin therapy; this may become severe or irreversible. A fatality has been reported. Predisposing conditions such as renal impairment, anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

Acute, subacute or chronic pulmonary reaction has been observed in patients treated with Macrodantin. If these reactions occur, the drug should be withdrawn and appropriate measures should be taken.

Insidious onset of pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) in patients on long-term therapy warrants close monitoring of these patients.

ADVERSE REACTIONS: Gastrointestinal reactions: Anorexia, nausea, emesis are the most frequent reactions; less frequently, abdominal pain and diarrhea; rarely, hepatitis. This dose-related toxicity reaction can be minimized by reduction of dosage, especially in the female patient.

Hypersensitivity reactions: Pulmonary sensitivity reactions, which can be acute, subacute, or chronic.

Acute reaction is commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on X-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and resolve with cessation of the drug therapy.

Subacute or chronic pulmonary reaction is associated with prolonged therapy. Insidious onset of malaise, dyspnea on exertion, cough, altered pulmonary function, and roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis or both are common manifestations. Impaired pulmonary function may result even after cessation of the drug therapy.

Dermatologic reactions: Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.

Other sensitivity reactions: Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, drug fever, and arthralgia.

Hematologic reactions: Hemolytic anemia, granulocytopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological reactions: Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.

Miscellaneous reactions: Transient alopecia. As with other antimicrobial agents, superinfections by resistant organisms may occur. With Macrodantin, however, these are limited to the genitourinary tract because suppression of normal bacterial flora elsewhere in the body does not occur.

DOSAGE AND ADMINISTRATION:

DOSAGE—Adults: 50-100 mg four times a day. Children: Should be calculated on the basis of 5-7 mg/kg of body weight per 24 hours to be given in divided doses four times a day (contraindicated under one month).

ADMINISTRATION: Macrodantin (nitrofurantoin macrocrystals) may be given with food or milk to further minimize gastric upset.

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

If the drug is to be used for long-term suppressive therapy, a reduction of dosage should be considered.

HOW SUPPLIED: Macrodantin (nitrofurantoin macrocrystals) is available in opaque, yellow capsules of 100 mg (coded "Eaton 009") and in opaque, yellow and white capsules of 50 mg (coded "Eaton 008") in bottles of 30, 100, 500, and 1,000 capsules; and in opaque, white capsules of 25 mg (coded "Eaton 007") in bottles of 100 capsules. Macrodantin Capsules, 50 mg and 100 mg, are also available in hospital unit-dose packages, strip-packaged in boxes of 100.

Furadantin (nitrofurantoin)/Macrodantin (nitrofurantoin macrocrystals) Sensi-Discs for the laboratory determination of bacterial sensitivity are available from BBL, Division of Bio-Quest. For information on simple nitrofurantoin assays in blood, serum, and urine, write or call the Medical Director. Literature sent to physicians on request.

For round-the-clock medical consultation on any Eaton product, phone Norwich, N.Y. 607-335-2111.

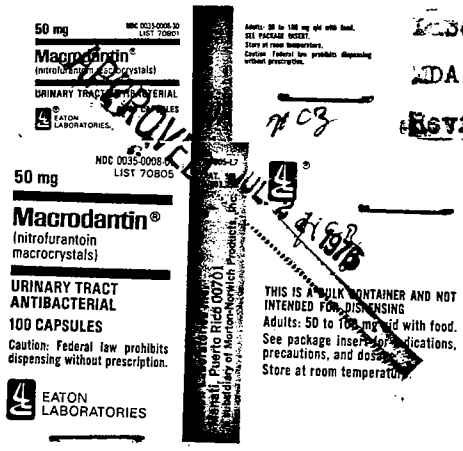
Eaton Laboratories Inc.
Manati, Puerto Rico 00701
a subsidiary of Morton-Norwich Products, Inc.

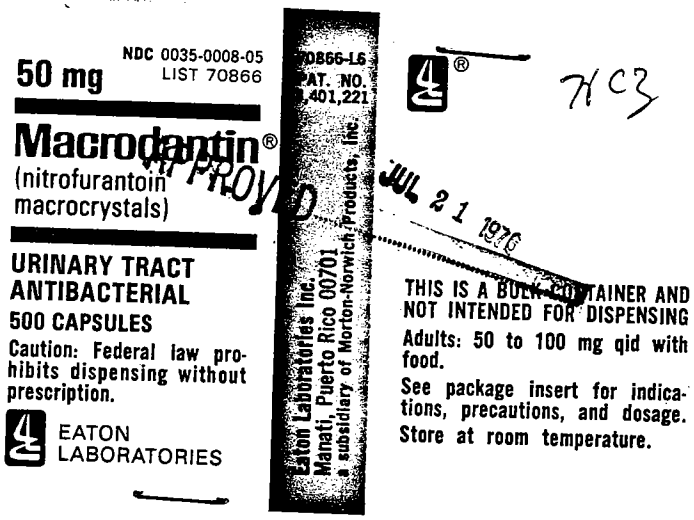
NOVEMBER 1973 PRINTED IN U.S.A.

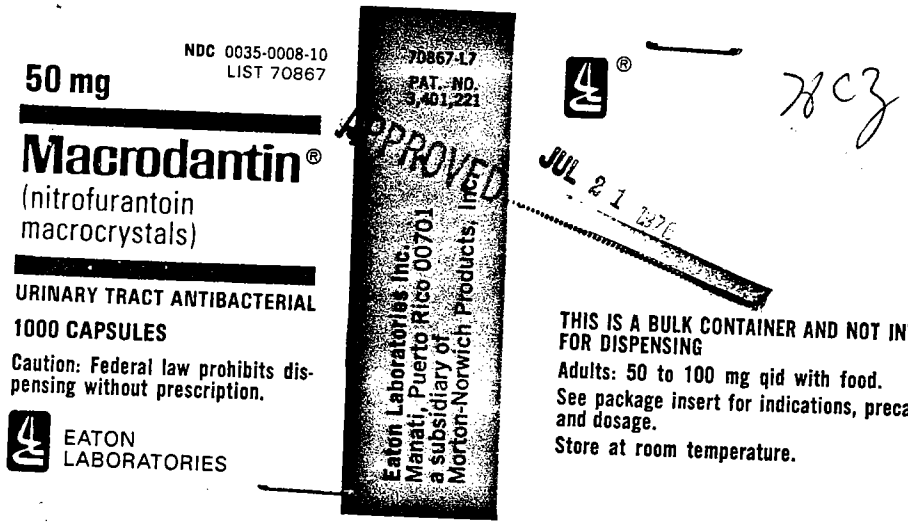
Labeling: Orig

NDA No: 16626 Rec'd 6-17-76

Reviewed By: H C Jeel 7/13/76



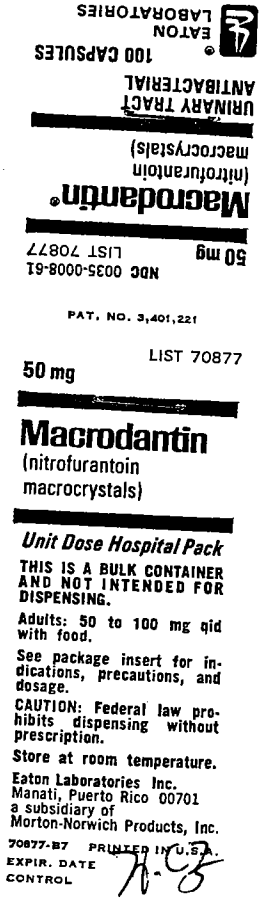




Labeling: Orig

NDA No: 16-620 S-3 10-18-76

Reviewed By: H.C. Zell 3/7/77



EATON LABORATORIES

100 CAPSULES

URINARY TRACT ANTIBACTERIAL

Macrodantin®
(nitrofurantoin macrocrystals)

50 mg

NDC 0035-0008-61 LIST 70877

PAT. NO. 3,401,221

LIST 70877

50 mg

Macrodantin
(nitrofurantoin
macrocrystals)

Unit Dose Hospital Pack

THIS IS A BULK CONTAINER AND NOT INTENDED FOR DISPENSING.

Adults: 50 to 100 mg qid with food.

See package insert for indications, precautions, and dosage.

CAUTION: Federal law prohibits dispensing without prescription.

Store at room temperature.

Eaton Laboratories Inc.
Manati, Puerto Rico 00701
a subsidiary of
Morton-Norwich Products, Inc.

70877-B7 PRINTED IN U.S.A.

EXPIR. DATE
CONTROL

H.C.Z

Labeling: Orig

NDA No: 16-620 10-18-76

Reviewed By: HC Zell 3/7/77

EATON LABORATORIES

100 CAPSULES

URINARY TRACT ANTIBACTERIAL

Macrodantin
(nitrofurantoin macrocrystals)

100 mg

NDC 0035-0009-61 LIST 70977

PAT. NO. 3,401,221

HC LIST 70977

100 mg

Macrodantin
(nitrofurantoin
macrocrystals)

Unit Dose Hospital Pack

THIS IS A BULK CONTAINER AND NOT INTENDED FOR DISPENSING.

Adults: 50 to 100 mg qid with food.

See package insert for indications, precautions, and dosage.

CAUTION: Federal law prohibits dispensing without prescription.

Store at room temperature.

Eaton Laboratories Inc.
Manati, Puerto Rico 00701
a subsidiary of
Morton-Norwich Products, Inc.

70977-B6 PRINTED IN U.S.A.

EXPIR. DATE

CONTROL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-017

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFD-140	16-620

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Norwich Pharmacal Company
Norwich, New York

4. AF NUMBER
9-700

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-017	3/17/76

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Macrodantin	nitrofurantoin macrocrystals

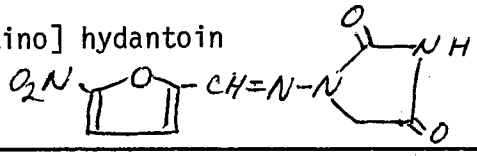
8. SUPPLEMENT(S) PROVIDES FOR:
Amendments presenting additional FPL reflecting the address of the new facility in Manatí, Puerto Rico.

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
10/12/76 (3)

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Antibacterial	☒ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY *(ies)*
Capsules	25,50 and 100 mg.

15. CHEMICAL NAME AND STRUCTURE
1-[(5-Nitrofurfurylidene)amino] hydantoin



16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS

S-017 was approved and a letter was issued 7/21/76.

The three supplemental amendments merely present additional FPL which has become available.

This NDA was approved 4/11/68.

18. CONCLUSIONS AND RECOMMENDATIONS

An acknowledge and retain letter should issue.

The labeling is satisfactory.

MPB 3/24/77 ARCasola, Ph. D 3/16/77

cc: HFD-140 HFD-140/HCZell/sj/3/14/77 HFD-140/ARCasola/3/8/77
HFD-140/CSO

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Howard C. Zell, Ph.D.	Howard C. Zell	3/7/77

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

CHEMIST'S REVIEW, Page 2 *Enter evaluation or comments for each item. If necessary, continue on 8" x 10½" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.*	NDA NUMBER 16-620

20. COMPONENTS AND COMPOSITION *(6, 7)*

NC

21. FACILITIES AND PERSONNEL *(8a,b)*

NC

22. SYNTHESIS *(8c)*

NC

23. RAW MATERIAL CONTROLS *(8d,e)*

a. NEW DRUG SUBSTANCE

NC

b. OTHER INGREDIENTS

NC

24. OTHER FIRM(S) *(8f)*

NC

25. MANUFACTURING AND PROCESSING *(8g,h,j,k)*

NC

26. CONTAINER *(8i)*

NC

27. PACKAGING AND LABELING *(8l,m)*

NC

28. LABORATORY CONTROLS *(In-Process and Finished Dosage Form) (8n)*

NC

29. STABILITY *(8p)*

NC

30. CONTROL NUMBERS *(8c)*

NC

31. SAMPLES AND RESULTS *(9)*

a. VALIDATION NA

b. MARKET PACKAGE NA

32. LABELING *(4)* Satisfactory.

Twelve copies of each type of labeling reflecting the address change to the new facility was submitted.

33. ESTABLISHMENT INSPECTION

NA

34. RECALLS

NA

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-140

2. NDA NUMBER: 16-620

3. NAME AND ADDRESS OF APPLICANT *(City and State)*:
Norwich Pharmacal Company
Norwich, New York 13815

4. AF NUMBER: 9-700

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-017	3/17/76

6. NAME OF DRUG: Macrodantin

7. NONPROPRIETARY NAME: nitrofurantoin macrocrystals

8. SUPPLEMENT(S) PROVIDES FOR:
Change of manufacturing facility, transfer of ownership of this NDA, an alternate manufacturing site and labeling reflecting the new facility.

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
6/16/76
7/9/76

10. PHARMACOLOGICAL CATEGORY: Antibacterial

11. HOW DISPENSED: [X] RX [ ] OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): Capsules

14. POTENCY *(ies)*: 25, 50 and 100 mg.

15. CHEMICAL NAME AND STRUCTURE
See insert.

16. RECORDS AND REPORTS
CURRENT: [ ] YES [ ] NO
REVIEWED: [ ] YES [ ] NO

17. COMMENTS

All of the requirements for changes in ownership of an NDA as stated in a memo from the Director, OSE, Dr. Marion J. Finkel, dated 8/15/74 are fulfilled in the submission and amendment.

See insert for continuation.

This NDA was approved 4/11/68.

18. CONCLUSIONS AND RECOMMENDATIONS
The submission meets the requirements of 21 CFR 314.8 (a)(2)(i)(iv) and (v), as well as those of the memo cited under item 17 above.

The supplement should be approved.

cc: HFD-140 HFD-140/HCZell/sj/7/16/76 HFD-140/CSO
HFD-140/ARCasola/7/14/76

7/20/76

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Howard C. Zell, Ph.D.	Howard C. Zell	7/13/76

DISTRIBUTION [ ] ORIGINAL JACKET [ ] REVIEWER [ ] DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

Enter evaluation or comments for each item. If necessary, continue on 8" x 10½" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.	NDA NUMBER 16-620

25. COMPONENTS AND COMPOSITION *(6, 7)*

NC

26. FACILITIES AND PERSONNEL *(8a,b)* Adequate

See Insert

27. SYNTHESIS *(8c)*

NC

28. RAW MATERIAL CONTROLS *(8d,e)*
a. NEW DRUG SUBSTANCE

NC

b. OTHER INGREDIENTS

NC

29. OTHER FIRM*(s)* *(8f)*

See Insert

30. MANUFACTURING AND PROCESSING *(8g,h,j,k)*

See Insert

31. CONTAINER *(8i)*

NC

32. PACKAGING AND LABELING *(8l,m)*

NC

33. LABORATORY CONTROLS *(In-Process and Finished Dosage Form)* *(8n)*

NC

34. STABILITY *(8p)*

See Insert

35. CONTROL NUMBERS *(8c)*

NC

36. SAMPLES AND RESULTS *(9)*

a. VALIDATION NA b. MARKET PACKAGE NA

37. LABELING *(4)*

See Insert

38. ESTABLISHMENT INSPECTION Satisfactory

See Insert

39. RECALLS

NA

WITHHOLD 2 PAGE(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-620 / S-017

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director, Division of Anti-Infective Drug Products (HFD-140)
Attn: R. C. Bieneman

DATE: April 30, 1976

FROM : Chief, Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing

SUBJECT: Approvable NDAs 8-693, Furadantin Tablets
16-620, Macrodantin Capsules

APPLICANT: Norwich Pharmacal Company
Norwich, N. Y.

PACKAGER: [redacted]

We have evaluated the operations of [redacted] as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) and the referenced New Drug Applications. We conclude that there is no reason to withhold approval of the referenced pending NDAs insofar as they relate to this firm and the type of operations as specified in these pending new drug applications.

Our evaluation is based in part on an inspection conducted 11/5-11/75.

David H. Bryant
David H. Bryant

cc: BUF-DO (HFR-2200)
CHI-DO (HFR-5100)
HFV-210
HFD-322 Firm File
HFD-300 R/F
HFD-140 (NDA Orig)
HFA-226
WABrown:nct:4/30/76

NDA 16-620/S-017

Norwich Pharmacal Company
Attention: Alexander B. Neill, Ph.D.
Norwich, New York 13815

MAR 28 1977

Gentlemen:

Reference is made to your communications of October 12, 1976, pertaining to your new drug application for Macrodantin (nitrofurantoin macrocrystals) Capsules.

Your communications provide labeling bearing the manufacturer's revised address.

The material submitted is being retained as part of your application for this article.

Sincerely yours,

MLG

Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Bureau of Drugs

cc: NYK-DO
Orig. NDA
HFD-140
HFD-140/CSO
HFD-140/HZellPh.D./3/7/77/ar/3/15/77 H.C.Z. 3/24/77

ACKNOWLEDGE & RETAIN A.C. Casola, Ph.D., 3/24/77

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 16-620

DATE APPROVAL LETTER ISSUED: JUL 21 1976

TO: Press Relations Staff *(CE-300)*

FROM: [X] Bureau of ~~Medicine~~ Drugs
[ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [ ] ABBREVIATED ORIGINAL NDA [X] SUPPLEMENT TO NDA

CATEGORY: [X] HUMAN [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Macrodantin nitrofurantoin macrocrystals

DOSAGE FORM: Capsules

HOW DISPENSED: [X] RX [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

Nitrofurantoin Macrocrystals	25 mg.
	50 mg.
	100 mg.

NAME OF APPLICANT *(Include City and State)*

Norwich Pharmacal Company
Norwich, New York 13815

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Antibacterial

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

Change of manufacturing facility, transfer of ownership of this NDA, an alternate manufacturing site and labeling reflecting the new facility.

FORM PREPARED BY

NAME: Howard C. Zell, Ph.D. Howard C. Zell DATE: 7/13/76

FORM APPROVED BY

NAME: Armand R. Casola, Ph.D. Armand R. Casola DATE: 7/20/76

FD FORM 1542 (7/69) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.