CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

80-816

Generic Name: Folic Acid 1mg Tablets

Sponsor: The Lannett Company, Inc.

Approval Date: May 6, 1974

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-816

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-816

APPROVAL LETTER

NDA 80-816

AF 25-995

The Lannett Company, Inc.
Attention: Mr. Samuel Gratz
9000 State Road
Philadelphia, PA 19136

MAY 0 6 1974

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Tablets, 1.0 mg.

We acknowledge receipt of your communications (two) dated March 4, 1974 enclosing (1) revised package inserts (2) additional manufacturing information and (3) an additional distributor with labels.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The enclosures summarize the conditions relating to the approval of this application.

Your application provides for distributors (names listed in a separate enclosure). We are enclosing with the copy of this letter to the distributors the conditions pertaining to the approval of this application.

Sincerely yours,

Paul A. Bryan, M.D.
Deputy Director for
Medical Activities
Office of Scientific Evaluation
Bureau of Drugs

cc:
PHI-DO
dup
HFD-107 HFD-106 HFD-100
HFD-8 HFD-13
OMCarroll/JLMeyer/JRoss
JLMeyer/MSeife init. 4/18/74
Enclosures
Records and Reports Requirement
Conditions of Approval of a New Drug Application
Final typing bho 4/30/74 Approval

JM Ross 5-2-74
OM Carroll 5/3/74
JLMeyer 5/3/74
M. Seife 5/6/74

9

List of Approved Distributors

Your application provides for you to label the drug with labels showing your distributors to be:

C. O. Truxton, Inc.
1458-60 Haddon Avenue
Camden, NJ 08103

American Pharmaceutical Company
201 Route 22
Hillside, NJ 07205

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-816

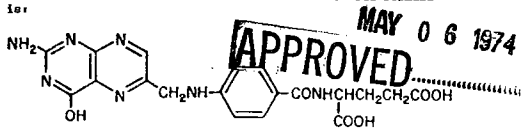
FINAL PRINTED LABELING

ORAL FOLIC ACID

JWR

DESCRIPTION

Folic acid is a yellow, odorless, crystalline powder; it is very slightly soluble in water; insoluble in alcohol, acetone benzene, chloroform and ether. The structural formula is:



MAY 0 6 1974
APPROVED

Folic Acid is available in 1.0 mg. tablets.

ACTIONS

Folic acid is necessary to prevent or reverse megaloblastic arrest of the bone marrow and the resulting macrocytic hyperchromic peripheral blood. Folic acid is not active as such, rather it is enzymatically reduced in the body to tetrahydrofolic acid(THFA), the coenzyme form that acts as an acceptor of various one carbon units.

INDICATIONS

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

ORAL ADMINISTRATION. Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

PARENTERAL ADMINISTRATION. Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe, or if gastrointestinal absorption may be, or is known to be, impaired.

USUAL THERAPEUTIC DOSAGE—IN ADULTS AND CHILDREN (REGARDLESS OF AGE) up to 1.0 mg. daily. Resistant cases may require larger doses.

MAINTENANCE LEVEL. When clinical symptoms have subsided and the blood picture has become normal, a maintenance level should be used, i.e.,0.1 mg. for infants and up to 0.3 mg. for children under four years of age, 0.4 mg. for adults and children four or more years of age, and 0.8 mg. for pregnant and lactating women, per day, but never less than 0.1 mg. per day. Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent.

In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.

HOW SUPPLIED

1.0 mg. tablets in bottles of 100 & 1000 tablets.

September, 1973

THE LANNETT COMPANY., INC.
9000 State Road
Philadelphia, Pa. 19136

ORAL FOLIC ACID

DESCRIPTION

Folic acid is a yellow, odorless, crystalline powder; it is very slightly soluble in water; insoluble in alcohol, acetone benzene, chloroform and ether. The structural formula is:

MAY 0 6 1974
APPROVED

Folic Acid is available in 1.0 mg. tablets.

ACTIONS

Folic acid is necessary to prevent or reverse megaloblastic arrest of the bone marrow and the resulting macrocytic hyperchromic peripheral blood. Folic acid is not active as such, rather it is enzymatically reduced in the body to tetrahydrofolic acid (THFA), the coenzyme form that acts as an acceptor of various one carbon units.

INDICATIONS

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

ORAL ADMINISTRATION. Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

PARENTERAL ADMINISTRATION. Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe, or if gastrointestinal absorption may be, or is known to be, impaired.

USUAL THERAPEUTIC DOSAGE—IN ADULTS AND CHILDREN (REGARDLESS OF AGE) up to 1.0 mg. daily. Resistant cases may require larger doses.

MAINTENANCE LEVEL. When clinical symptoms have subsided and the blood picture has become normal, a maintenance level should be used, i.e.,0.1 mg. for infants and up to 0.3 mg. for children under four years of age, 0.4 mg. for adults and children four or more years of age, and 0.8 mg. for pregnant and lactating women, per day, but never less than 0.1 mg. per day. Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent.

In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.

HOW SUPPLIED

1.0 mg. tablets in bottles of 100 & 1000 tablets.

September, 1973

NDC-463-6096-10

1000 TABLETS

FOLIC ACID

TABLETS, U.S.P.

1 mg.

Usual* Daily Dosage--
Therapeutic: 0.25 mg. to 1.0 mg.
Maintenance: 0.1 mg. to 0.25 mg.
*Resistant cases may require larger doses (see insert).

CAUTION: Federal law prohibits dispensing without prescription.

See insert for full particulars

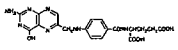
C. O. TRUXTON Inc.
DISTRIBUTORS
Pharmaceuticals
Camden New Jersey 08103

Lot No.

ORAL FOLIC ACID

DESCRIPTION

Folic acid is a yellow, odorless, crystalline powder it is very slightly soluble in water; insoluble in alcohol, acetone benzene, chloroform and ether. The structural formula is:



Folic Acid is available in 1.0 mg. tablets.

ACTIONS

Folic acid is necessary to prevent or reverse megaloblastic arrest of the bone marrow and the resulting macrocytic hyperchromic peripheral blood. Folic acid in not active as such, rather it is enzymatically reduced in the body to tetrahydrofolic acid (THFA), the coenzyme form that acts as an acceptor of various one carbon units.

INDICATIONS

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid expecially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

Oral administration: Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

Usual therapeutic dosage: In adults: 0.25 mg. to 1.0 mg. daily. In Children (regardless of age): 0.25 to 1.0 mg. daily. Resistant cases may require larger doses.

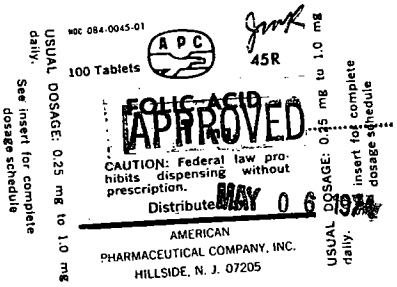
Maintenance dosage: When clinical symptoms have subsided and the blood picture has become normal, a maintenance dose of 0.1 mg. to 0.25 mg. daily should be used, but never less than 0.1 mg. per day. Patients should be kept under close supervision and adjustment of the maintenance dose made if relapse appears imminent.

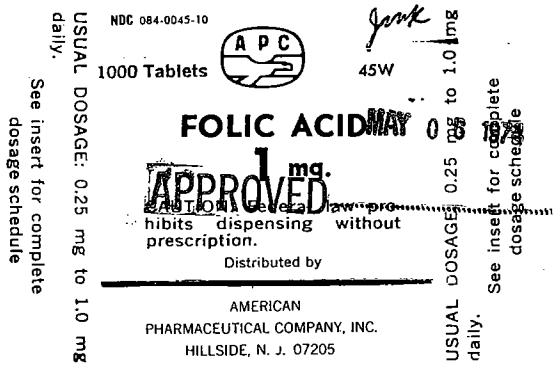
In the presence of alcoholism, pregnancy, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance dose should be at least doubled.

HOW SUPPLIED

1.0 mg. tablets in bottles of 100 & 1000 tablets.

Sept. 1971


NDC 084-0045-01
A P C
100 Tablets
45R
FOLIC ACID
1 mg.
APPROVED
CAUTION: Federal law prohibits dispensing without prescription.
Distributed MAY 0 6 1974
AMERICAN
PHARMACEUTICAL COMPANY, INC.
HILLSIDE, N. J. 07205
USUAL DOSAGE: 0.25 mg to 1.0 mg daily. See insert for complete dosage schedule
USUAL DOSAGE: 0.25 mg to 1.0 mg daily. See insert for complete dosage schedule


NDC 084-0045-10
A P C
1000 Tablets
45W
FOLIC ACID
1 mg.
APPROVED
MAY 0 6 1974
CAUTION: Federal law prohibits dispensing without prescription.
Distributed by
AMERICAN
PHARMACEUTICAL COMPANY, INC.
HILLSIDE, N. J. 07205
USUAL DOSAGE: 0.25 mg to 1.0 mg daily. See insert for complete dosage schedule
USUAL DOSAGE: 0.25 mg to 1.0 mg daily. See insert for complete dosage schedule


USUAL DOSAGE: 0.25 mg to 1.0 mg daily.
See insert for complete dosage schedule
1000 Tablets
List No. 1098
FOLIC ACID
1 mg.
CAUTION: Federal law prohibits dispensing without prescription.
THE LANNETT COMPANY, INC.
Ethical pharmaceuticals for the professon
PHILADELPHIA, PA. 19136
MADE IN U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-816

CHEMISTRY REVIEW(S)

REVIEW OF ANDA

DATE COMPLETED: 1/12/72

ANDA #: 80-816

F.R. Date: 4/9/71
The Lannett Company, Inc.
9000 State Road
Philadelphia, Pa. 19136

NAME OF DRUG: Trade & Generic: Folic Acid Tablets, 1 mg., in bottles of 100 & 1,000 tablets.

DATE OF SUBMISSION: 12/23/71

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies: To be review by chemist.

2. Review of Labeling:

   a. Container Labels: Satisfactory.

   b. Package Insert: Insert a period or semicolon following the word"powder" in the first line. If a period is selected capitalize the letter "I" in the word "it" following.

   In the third line in ACTIONS change the word "in" to "is".

CONCLUSIONS: 1. Studies require chemist review.
2. Container labels are satisfactory.
3. Package insert requires grammatical corrections.

RECOMMENDATIONS: 1. Chemist to review.
2. Approve container label.
3. Require grammatical corrections in insert.

John H. Eilert, M.D.

cc:
Dup.
BD-69
JHEilert/mc/2/8/72

REVIEW OF ~~ANDA,~~ AMENDMENT

DATE COMPLETED: 1-24-73

ANDA #: 80-816

F.R. DATE: 4-9-73

CO. NAME: The Lannett Company, Inc.
9000 State Road
Philadelphia, Pa. 19136

NAME OF DRUG: Trade: Folic Acid Toblets, 1 mg. U.S.P.,
& in bottles of 1,000 tablets
Generic:

DATE OF SUBMISSION: 11-13-72

TYPE OF SUBMISSION: New distributor, C. O. Truxton, Inc.
1458-60 Haddon Avenue
Camden, N. J. 08103

CLINICAL EVALUATION:

1. Review of Commitment: For chemist review.

2. Review of Labeling:

Container label approvable.

Insert (Sept. 1971) continues errors detailed in FDA 3-31-72 communication.

CONCLUSION: New distributor.

RECOMMENDATIONS: Request response to 3-31-72 communication and advise insert corrections in new printing.

John H. Eilert, M.D.
John H. Eilert, M.D.

cc:
Dup
BD-69
JHEilert/rt/1-29-73

REVIEW OF RESUBMISSION

DATE COMPLETED: 4-1-74

ANDA #: 80-816

F.R. DATE: 4-9-71

CO. NAME: The Lannett Co., Inc.
9000 State Rd.
Philadelphia, PA 19136

NAME OF DRUG: Folic Acid Tablets, 1 mg.

DATE OF SUBMISSION: 3-4-74

TYPE OF SUBMISSION: Resubmission

CLINICAL EVALUATION:

1. Review of Studies: None submitted

2. Review of Labeling: Changes made as suggested in letter of March, 1972.

3. Controls revised as requested.

4. Environmental impact statement submitted to be reviewed by the chemist.

CONCLUSIONS:
1. Revisions done as suggested in March 1972.
2. Environmental impact statement submitted to be reviewed by the chemist.

RECOMMENDATIONS: See conclusions.

O.M. Carroll, M.D.

cc:
Dup
HFD-107
OMCarroll/wlb/4-2-74

REVIEW OF ~~SUPPLEMENT~~ Amendment

DATE COMPLETED: 4-1-74

ANDA #: 80-816

F.R. DATE: 4-9-71

CO. NAME: The Lannett Co., Inc.
9000 State Rd.
Philadelphia, PA 19136

NAME OF DRUG: Folic Acid Tablets, 1 mg.

DATE OF SUBMISSION: 3-4-74

TYPE OF SUBMISSION: ~~Supplement~~ Amendment, additional distributor

CLINICAL EVALUATION:

1. Review of Studies: None submitted

2. Review of Labeling: No change

3. New distributor: American Pharmaceutical Co.
Hillside, NJ 07702- 07205

CONCLUSIONS: New distributor as noted above.

RECOMMENDATIONS: NONE

O.M. Carroll M.D.
O.M. Carroll, M.D.

cc:
Dup
HFD-107
OMCarroll/wlb/4-2-74

CHECKLIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION (OR SUPPLEMENT)

Federal Register Statement Date: 4/9/71

NDA Number: 80-816

Name and Address of Applicant (City and State)

The Lannett Company, Inc.
Phil. P. 19136

Original: XX
Amendment:
Supplement:
Other:

Name of Drug	Nonproprietary Name
	Folic Acid

DATE(s) of Submission(s)

Purpose of Supplement

Pharmacological Category	How Dispensed	AF Number
Vitamin	[X] Rx [ ] OTC	25-995
Dosage Form(s)	Potency(ies)	Related IND/NDA/MF
Tablet	1 mg.	

Satisfactory [ ] Labeling
Date Due Revise per M.O.

Satisfactory [ ] Components, Composition, Manufacturing and Controls
Date Due See below

Satisfactory [ ] Biologic Availability
Date Due NA
Is data on current formulation? YES [ ] NO [ ]

APPEARS THIS WAY ON ORIGINAL

Satisfactory [ ] Probably or Possibly Effective Indications (if in Labeling)
Date data Due

Establishment Inspection	Recalls
EI 8/17-30/71 Unsatisfactory	

Is relabeling of drug in commercial channels required? [ ] YES [X] NO
If so, what level:

Remarks

1. Correct package insert grammar.
2. GMP certification statement in proper form.
3. Folic acid- —— and assay tests not performed.
4. ——————————————————
5. Final dosage form - content uniformity and assay do not follow USP XVIII procedure.
6. Follow 130.4(f) instead of referring to DMR
7. Unsatisfactory EI

Conclusions

Rev. W/F

REJoyce 3/24/72

REJoyce 3/13/72

Reviewer	Signature	Date Completed

NDA SUMMARY

ame & Address of Applicant (City & State) the lannett company philadelphia, pa 19136	SUPPLEMENT ☐
	NDA Number 80-815
	Supplement Date and Num...
me of Drug	Nonproprietary Name: folic acid
	Amendment Date(s): 11/13/73
rpose of Supplement	Other Date(s)
armacological Category: vitamin	How Dispensed: Rx [XX] O.T.C. ☐
	AF Number 25-995
age Form(s): tablet	Potency (ies): 1.0 mg.
	Related IND/NDA/DF(s)

isfactory ☐ Labeling Date Due ____ as per MO's review(jheilert)

isfactory ☐ Components, Composition, Manufacturing and Controls Date Due ____ see below

isfactory ☐ Biologic Availability Date Due ____ NA

Is data on current formulation? YES ☐ NO ☐

is. tory ☐ Probably or Possibly Effective Indications (if in labeling) Date Data Due ____

APPEARS THIS WAY ON ORIGINAL

blishment Inspection: not in compliance: PHI-DO 3/5/71

Recalls

elabeling of drug in commercial channels required? YES ☐ NO ☐

o, what level:

rks

Request: 1. revised insert, as per MO's review within 180 days
2. all mfg information rewuested 3/31/72

usions rev w/f

Chill 4/25/73
gmillar

ER: SIGNATURE: DATE:

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date 4-9-71

NDA Number 80-816

AF Number 25-995

Original
Amendment X
Supplement
Resubmission
Correspondance
Report
Other

Name and Address of Applicant (City and State)

The Lannett Company, Inc.
9000 State Road
Philadelphia, Pennsylvania 19136

Date(s) of Submission(s)

Purpose of Amendment/Supplement
1. submission of revised package inserts, additional manufacturing information and additional distributor with labels

3-4-74

Pharmacological Category	Name Of Drug	
Vitamin	Folic Acid	
Dosage Form(s)	Potency	How Dispensed
tablet	1.0 mg.	Rx X OTC
Environmental Impact Analysis Report	Samples	Related IND/NDA/MF(s)
submitted 3-4-74		

Labeling

Satisfactory (OMCarroll)

Biologic Availability

NA

APPEARS THIS WAY ON ORIGINAL

Establishment Inspection

The Lannett Co. Inc. in complaince 10/17-31 & 11/1,16/73

Components, Composition, Manufacturing and Controls

Satisfactory

Remarks

Additional Distributor

American Pharmaceutical Company
201 Route 22
Hillside, New Jersey 07205

Conclusion Approved

Reviewer: J.M.Ross

J.M. Ross 4-24-74

Date:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-816

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant The Lannett Company Inc.

Address 9000 State Road, Philadelphia, Pa. 19136

Date December 23, 1971

Name of new drug Folic Acid Tablets 1 mg.

☐ Original application (regulation § 130.4).

☐ Amendment to original, unapproved application (regulation § 130.7).

☒ Abbreviated application (regulation § 130.4(f)).

☐ Amendment to abbreviated, unapproved application (regulation § 130.7).

☐ Supplement to an approved application (regulation § 130.9).

☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with § 1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of § 130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in § 130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in § 130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form).

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance; for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. *a.* An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW, Food and Drug Administration, Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

THE LANNETT COMPANY, INC.
(Applicant)

Per [signature]
(Responsible official or agent)

Samuel Gratz
President
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

only

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 80-816

DATE APPROVAL LETTER ISSUED: MAY 0 6 1974

TO: Press Relations Staff *(PA-40)*

FROM: [X] Bureau of Drugs

APPROVAL OF ORIGINAL ABBREVIATED NDA

ATTENTION

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

Abbreviated

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

CATEGORY: [X] HUMAN [ ] VETERINARY

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

Folic Acid

DOSAGE FORM: tablet

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.)*

Folic Acid 1.0 mg.

APPEARS THIS WAY ON ORIGINAL

NAME OF APPLICANT *(include City and State)*

The Lannett Company, Inc.
9000 State Road
Philadelphia, Pennsylvania 19136

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Vitamin

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: J.M.Ross — DATE:

FORM APPROVED BY

NAME: J.I. Meyer — DATE:

Form FD 1642 (4/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 4/12/73
FROM: gerry millar (thru Jack L. Meyer)		OFFICE BD-69
TO: Mr. B.T. Loftus, Dep. Dir. Office of Compliance		DIVISION BD-300
SUBJECT: collaborative draft(s)		

SUMMARY

; In connection with NDA 80-816 for folic acid tablets

The applicant the lannett co
phila, pa 19136

AF 25-995

We acknowledge receipt on 11/27/72 of amendment dated 11/13.72 for distributor

In accordance with the 2/27/73 directive, Office of Compliance a request is made for:

REQUESTED

○ 1. establishment inspection report on

☐ a. the applicant

☐ b. others

○ ***** 2. evaluation of compliance with CGMPR

○ 3. recommendation for approval/disapproval of the application/communication/supplement based on your evaluation of compliance with CGMPR

PLEASE EXPEDITE

SIGNATURE	DOCUMENT NUMBER 80-816

FD FORM 2034 (2/72)

[DESI 5897; Docket No. FDC-D-265; NDA 5-897, etc.]

FOLIC ACID PREPARATIONS, ORAL AND PARENTERAL FOR THERAPEUTIC USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following folic acid preparations:

1. a. Folvite Elixir; 5 mg. folic acid per 5 cc.;

b. Folvite Tablets; 5 mg. and 20 mg. folic acid per tablet; and

c. Folvite Parenteral Solution; sodium folate equivalent to 15 mg. folic acid per cc.; marketed by Lederle Laboratories, Pearl River, New York 10965 (NDA 5-897).

2. Folic Acid Tablets; 5 mg. per tablet; marketed by Eli Lilly and Co., Box 618, Indianapolis, Indiana 46206 (NDA 6-135).

3. Folic Acid Injection; 15 mg. folic acid, as the sodium salt, per cc.; marketed by S. F. Durst and Co., Inc., 5317 North Third Street, Philadelphia, Pennsylvania 19120 (NDA 6-338).

In addition to the above products, folic acid preparations for therapeutic use are marketed by other firms. A partial list of other suppliers of folic acid preparations limited to prescription dispensing, as indicated in readily available reference sources, is as follows:

ABA Pharmaceutical Co., Division of Bergher Distributing Co.
American Pharmaceutical Co.
American Drug Products.
American Quinine Co.
Approved Pharmaceutical Corp.
Arcum Pharmaceutical Corp.
Associated Labs., Inc.
Barre Drug Co., Inc., The.
Barry-Martin Pharmaceuticals, Inc.
Bell Pharmacal Co.
Carroll Chemical Co., The.
Columbia Medical Co.
Consolidated Midland Corp., CMC Research Division.
Corvit Pharmaceuticals.
Daniels, Robert and Co., Inc.
DuMont Pharmacal Co.
Evron Pharmaceutical Co., Inc.
Faraday Laboratories, Inc.
Gold Leaf Pharmacal Co., Inc.
Gotham Pharmaceutical Co., Inc.
Halsey Drug Co., Inc.
Harvey Labs., Inc.
Jan Labs.
Kirkman Labs., Inc.
Lannett Co., Inc.
Lit Drug Co.
Lustgarten Laboratories, Inc.
Mifflin, McCambridge Co., Inc.
Penhurst Pharmacal Co.
Pharmex, Inc.
Preston Franklin Pharmacal Co.
Richlyn Labs.
Robinson Laboratory, Inc.
Spencer-Mead, Inc.
Stanlabs, Inc.
Supreme Pharmaceutical Co., Inc.
Thompson, Wm. T., Co.
Towne, Paulson and Co., Inc.
Vitamin Research Corp.
Vita-Fore Products Co.
West-Ward, Inc.
Williams Chemical Co.
Winsale Drug Co.

The drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new-drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new-drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new-drug applications and supplements to previously approved new-drug applications under conditions described in this announcement.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. Folic acid is effective for the treatment of megaloblastic anemias of tropical and nontropical sprue, nutritional origin, pregnancy, infancy, and childhood.

2. There is a lack of substantial evidence that folic acid is effective for the following labeled indications: "macrocytic anemias associated with pellagra and similar deficiency states" and such vague, unspecific conditions as "macrocytic anemia of gastrointestinal origin" and "megaloblastic anemias other than pernicious anemia."

The Food and Drug Administration also concludes that there is no evidence that doses of folic acid greater than 1 mg. daily have greater efficacy than do those of 1 mg. Further, the usual therapeutic dose, oral or parenteral, should be 0.25 mg. to 1.0 mg. daily, and the maintenance dose should ordinarily be 0.1 to 0.25 mg. daily. Administration of higher doses greatly increases the possibility of masking vitamin B-12 deficiencies and the insidious development of or precipitation of neurological manifestations and/or lesions.

Preparations supplying no more than 0.1 mg. folic acid daily continue to be regarded as dietary supplements (21 CFR 3.42) and may be prescribed when a maintenance dose of 0.1 mg. a day is indicated.

B. *Form of drug.* Folic acid preparations are in (1) tablet form suitable for oral administration and contain no less than 0.15 mg. and no more than 1.0 mg. folic acid per tablet or (2) solution form suitable for parenteral administration in the dosages recommended in the labeling guidelines below.

C. *Labeling conditions.* 1. The label bears the statement "CAUTION: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations promulgated thereunder, and those parts of its labeling indicated below are substantially as follows: (Optional additional information, applicable to the drug, may be proposed under other appropriate paragraph headings and should follow the information set forth below.)

FOLIC ACID

DESCRIPTION

(To be supplied by the manufacturer. This is to be confined to an appropriate description of the physical and chemical properties of the drug, and the formulation.)

ACTIONS

(To be supplied by the manufacturer. This is to be confined to an appropriate statement of the demonstrated pharmacologic/physiologic actions of the active ingredients of the drug in humans. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

Oral administration: Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

Parental administration: Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe, or if gastrointestinal absorption may be, or is known to be, impaired.

Usual therapeutic dosage: In adults: 0.25 mg. to 1.0 mg. daily. *In Children (regardless of age)*: 0.25 to 1.0 mg. daily. Resistant cases may require larger doses.

Maintenance dosage: When clinical symptoms have subsided and the blood picture has become normal, a maintenance dose of 0.1 mg. to 0.25 mg. daily should be used, but never less than 0.1 mg. per day. Patients should be kept under close supervision and adjustment of the maintenance dose made if relapse appears imminent.

In the presence of alcoholism, pregnancy, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance dose should be at least doubled.

D. *Previously approved applications.* 1. Each holder of a "deemed approved" new-drug application (i.e., an application which became effective on the basis of safety prior to October 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform to the labeling conditions described herein for the drug, and complete current container labeling, unless recently submitted.

b. Updating information as needed to provide for an oral dosage form containing no less than ~~0.5~~ 0.15 mg. and no more than 1.0 mg. folic acid per tablet or a

parenteral dosage form containing an amount appropriate for administration as described herein, and to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new-drug application form FD–356H to the extent described for abbreviated new-drug applications, § 130.4(f), published in the FEDERAL REGISTER April 24, 1970 (35 F.R. 6574). (One supplement may contain all the information described in this paragraph.)

2. Such supplements should be submitted within the following time periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling; or, for those products which must be reformulated, 180 days for revised labeling fully in accord with this announcement, provided claims for which substantial evidence of effectiveness is lacking are deleted within 60 days. The supplements should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 180 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs 1 and 2 are acted upon, provided that the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement wthin the time periods described in subparagraph 2a.

E. *New applications.* 1. Any person who distributes or intends to distribute such drug which is intended for the conditions of use for which it has been shown to be effective, as described under A1 above, should submit an abbreviated new-drug application meeting the conditions specified in § 130.4(f) (1) and (2), published in the FEDERAL REGISTER April 24, 1970 (35 F.R. 6574). Such applications should include proposed labeling which is in accord with the labeling conditions described herein.

2. Distribution of any such preparation currently on the market without an approved new-drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein, except that if the preparation must be reformulated, 180 days will be allowed for the dosage recommendations to be in accord with this announcement.

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of this publication, a new-drug application to the Food and Drug Administration.

c. The applicant submits within a reasonable time additional information that may be required for the approval of the application as specified in a written communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

F. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new-drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraph A2 of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Promulgation of the proposed order would cause any such drug for human use offered for the indications for which substantial evidence of effectiveness is lacking, to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing, together with a well-organized and full-factual analysis of the clinical and other investigational data the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety. If a hearing is requested and justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

G. *Unapproved use or form of drug.* 1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it may be regarded as an unapproved new drug subject to regulatory proceedings until such recomended use is approved in a new-drug application, or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for use other than the use provided for in this announcement, appropriate additional information as described in § 130.4 or § 130.9 of the regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth herein. Requests for such meetings should be made to the Office of Scientific Evaluation at the address given below, within 30 days after the publication of this notice in the FEDERAL REGISTER.

A copy of the NAS–NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 5897, directed to the attention of the following appropriate office, and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD–100), Bureau of Drugs.

Original abbreviated new-drug applications (identify as such): Drug Efficacy Study Implementation Project Office (BD–5), Bureau of Drugs.

Request for Hearing (identify with Docket number): Hearing Clerk, Office of General Counsel (GC–1), Room 6–62, Parklawn.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD–5), Bureau of Drugs.

Requests for NAS–NRC report: Press Relations Office (CE–200), 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: March 19, 1971.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.71–4952 Filed 4–8–71;8:46 am]

[DESI 10423]

LEVALLORPHAN TARTRATE INJECTION

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drug for intravenous use:

Lorfan Injection, containing levallorphan tartrate; Roche Laboratories, Division of Hoffman-LaRoche, Inc., 340 Kingsland Street, Nutley, New Jersey 07110 (NDA 10–423).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-816

CORRESPONDENCE

THE LANNETT COMPANY, INC.

Manufacturing Pharmaceutical Chemists

9000 STATE ROAD
PHILADELPHIA, PA. 19136

80-816

December 23, 1971

ABBREVIATED
NEW DRUG APPLICATION

Food and Drug Administration
Bureau of Drugs
Rockville, Md. 20852

Ref: A.N.D.A. - Folic Acid Tablets 1 Mg.

Gentlemen:

In accordance with the statement published by the Administration in the Federal Register Friday April 9, 1971 page 6843-6844. We enclose in triplicate an A.N.D.A. for our product Folic Acid Tablets 1 mg.

Should additional information be required, such information will be submitted in a reasonable length of time.

Sincerely yours,

THE LANNETT COMPANY, INC.

Samuel Gracz, Pres.
President

SG/wn

RECEIVED DEC 23 1971 BUREAU OF DRUGS

RECEIVED 1 COPY
PHOTOSTATS OF
COVER LETTER MADE
FOR DUP____TRIP____

NDA 80-816

AF 25-995

JAN 11 1972

The Lannett Company, Inc.
Attention: Mr. Samuel Gratz
9000 State Road
Philadelphia, Pennsylvania 19136

Gentlemen:

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

NAME of DRUG: Folic Acid Tablets, 1 mg.

DATE of APPLICATION: December 23, 1971

DATE of RECEIPT: December 30, 1971

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

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

Sincerely yours,

Oree M. Carroll M.D. 1/11/72.

Oree M. Carroll, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
PHI-DO
Dup
BD-67
BD-69
BD-22 JLMeyer 1/10/72
BD-310
JLMeyer/sam/1/5/72
Ack.

NDA 80-816

AF 25-995

The Lannett Company, Inc.
Attention: Mr. Samuel Gratz
9000 State Road
Philadelphia, Pennsylvania 19136

MAR 31 1972

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Tablets, 1 mg.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

1. At the time of the next printing revise the package insert as follows:

   a) Insert a semicolon after the word "powder" in the first line.
   b) In the ACTIONS section: Change the word "in" to "is" in the third line.

2. Include a certification statement from The Lannett Company, Inc. that the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of the drug are in conformity with current good manufacturing practice in accord with Part 133 (21 CFR) of the regulations.

3. Procedures that assure the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or, if not listed or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality, and purity. The following deficiencies are noted:
   a) The assay and ——— tests are not performed on the active ingredient, folic acid.

APPEARS THIS WAY
ON ORIGINAL

b) _____

c) The content uniformity and assay tests do not follow the USP XVIII procedures. If the alternate method is used, data should be submitted to show its comparability with the compendium procedure.

4. Submit an outline for the following:

a) Specific procedures for processing and packing the drug.
b) Label and labeling control procedures.

Please submit the above information promptly.

In future submissions of abbreviated new drug applications, we recommend you comply with Section 130.4(f) as published in the Federal Register of April 24, 1970, rather than refer to a master file.

Information in a report of inspections of your facilities, by inspectors of this Administration (covering the methods, facilities, and controls used), indicates that there is disagreement between actual current good manufacturing practice and the commitment made in your application.

Therefore, before we can take final action on this abbreviated new drug application, we should have a satisfactory inspection report.

Copies of this letter have been sent to our Philadelphia District Office. We recommend that you contact the District and arrange for an inspection after the deficiencies have been corrected.

Sincerely yours,

Margaret Clark MD for

Marvin Seife, M.D. 3/30/72
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
PHI-DO
Dup
BD-69 BD-67
BD-22 BD-242

JHEilert/JLMeyer/REJoyce: 3/13/72
R/D init. MAClark, JLMeyer 3/27/72
Final typing bhy 3/30/72
Rev. W/F

JLMeyer 3/30/72

REJoyce 3/30/72

NDA ORIG AMENDMENT E

THE LANNETT COMPANY, INC.
Manufacturing Pharmaceutical Chemists

FPL

DEPARTMENT
OF RESEARCH AND
DEVELOPMENT

9000 STATE ROAD
PHILADELPHIA, PA. 19136

ORIG

November 13, 1972

Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Md. 20852

RE: N.D.A. 80-816; Folic Acid Tablets Supplement for C. O. Truxton, ~~Inc.~~

Gentlemen:

We would like to supplement our N.D.A. 80-816 for Folic Acid Tablets to provide that we manufacture, package and label the drug for C. O. Truxton, Inc. 1458-60 Haddon Ave. Camden, New Jersey 08103 under their private label.

Enclosed are the following:

1. Distributors statement
2. 12 labels for bottles of 1000 tablets. C. O. Truxton, Inc. will not offer bottles of 100 tablets at this time.
3. Inserts

RECEIVED 1 COPY
PHOTOSTATS MADE
FOR DUP_____TRIP_____

Sincerely yours,

THE LANNETT COMPANY, INC.

Samuel Gratz, B.Sc.
President

RECEIVED
NOV 1972
BUREAU OF DRUGS

Encl.
BW:ng

NDA 80-816
AF 25-995

APR 30 1973

The Lannett Company, Inc.
Attention: Mr. Samuel Gratz
9000 State Road
Philadelphia, Pennsylvania 19136

Gentlemen:

Reference is made to your abbreviated new drug application dated July 20, 1971, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Tablets, 1.0 mg.

We acknowledge receipt of a communication dated November 13, 1972, amending the application.

Reference is also made to our letter dated March 31, 1973, reviewing your abbreviated new drug application.

Your application, as amended, provides for you to label 1000 tablet containers of the drug with a label showing the distributor to be:

C. O. Truxton, Inc.
Camden, New Jersey 08103

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

1. A revised package insert, in accord with the comments transmitted to you on March 31, 1972. This revision, however, may be made at the time of the next printing (180 days).

2. The manufacturing information also requested on March 31, 1972.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 4/27/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
PHI-DO
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R/D init. JMeyer/4-12-73
Final typing/rt/4-25-73
rev w/f

JHEilert 4-26-73

JLMeyer 4/26/73

Rev. WK, C
Original

THE LANNETT COMPANY, INC.
MANUFACTURING PHARMACEUTICAL CHEMISTS
9000 STATE ROAD ❦ PHILADELPHIA, PENNA. 19136

RESUBMISSION
NDA ORIG AMENDMENT

OFFICE OF PRESIDENT

March 4, 1974

FPL

Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Md. 20852

RE: NDA 80-816; Folic Acid Tablets 1 mg.

Gentlemen:

This is in response to your letter of comment dated March 31, 1972 concerning our NDA 80-816, Folic Acid Tablets, 1 mg.

Enclosed are the following:

1. Revised insert, in accordance with your letter of comment and your announcement F.R. Vol. 38, No. 148 - Thursday, August 2, 1973, entitled "Folid Acid Preparations, Oral and Parenteral for Therapeutic Use."

2. Certification statement from the applicant.

3. Revised "Methods of Testing and Specifications for Acceptance" for

   a. Raw Materials
      (1) Folic Acid
      (2) ---
      (3) ———

   b. Finished Drug - Folic Acid Tablets 1 mg.

4. An outline of the procedures for processing and packing the drug; and, labeling control procedures.

5. Environmental Impact Analysis Report.

We trust that we have submitted all the information requested in your letter of comment.

RECEIVED 1 COPY
PHOTOSTATS MADE
FOR DUP ✓ TRIP

Sincerely yours,
THE LANNETT COMPANY, INC.

Samuel Gratz, B.Sc.
President

SG:jb/encls.

RECEIVED MAR 1974 FOOD AND DRUG ADMINISTRATION

Original

THE LANNETT COMPANY, INC.
MANUFACTURING PHARMACEUTICAL CHEMISTS
9000 STATE ROAD ❦ PHILADELPHIA, PENNA. 19136

OFFICE OF PRESIDENT

NDA ORIG AMENDMENT

March 4, 1974

FPL

Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Md.20852

Re: NDA 80-816; Folic Acid Tablets 1 mg.
Supplement for American Pharmaceutical Co.

Gentlemen:

We desire to supplement our NDA 80-816, Folic Acid Tablets, 1 mg. to provide for us to manufacture, package and label the drug, under private label for The American Pharmaceutical Company, 201 Route 22, Hillside, N.J. 07205.

Enclosed are the following:

1. Distributor's statement in triplicate.
2. Twelve labels for 100 tablets; twelve labels for 1000 tablets.
3. Twelve inserts.

Sincerely yours,

THE LANNETT COMPANY, INC.

Samuel Gratz, B.Sc.
President

SG:jb
encls.

RECEIVED 1 COPY
PHOTOSTATS MADE
FOR DUP ✓ TRIP ✓

RECEIVED MAR 6 1974 BUREAU OF DRUGS