CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

83-141

Generic Name: Folic Acid 1mg Tablets

Sponsor: Bolar Pharmaceutical Company, Inc.

Approval Date: February 15, 1973

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-141

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
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:

83-141

APPROVAL LETTER

NDA 83-141
AF 10-156

FEB 15 1973

Bolar Pharmaceutical Company, Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, New York 11726

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.

Reference is also made to your communication dated December 15, 1972, enclosing printed labeling.

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 130.9 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.

At the time of the next printing, however, it is recommended that the package insert be revised to include a reference to the 100 tablet container in the HOW SUPPLIED section.

Please submit twelve copies of the revised insert when available.

Sincerely yours,

R W Duncan Jr. 2/13/73

Paul A. Bryan, M.D.
Director
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc: NYK-DO
Dup
BD-69 BD-66 BD-100
BD-106 BD-242
JHEilert/JLMeyer/RJWolters
R/D init. MAClark, JLMeyer 2/6/73
Enclosures
Records and Reports Requirement
Conditions of Approval of a New Drug Application
Final typing bhy 2/8/73 Approved

JHEilert 2-9-73

RJ Wolters 2-8-73 JLMeyer 2/12/73 M. Clark, MD 2/13/73

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-141

FINAL PRINTED LABELING

APPROVED FEB

FOLIC ACID

DESCRIPTION: Folic Acid is a yellow or yellowish orange, odorless, crystalline powder, It is very slightly soluble in water; insoluble in alcohol, chloroform and ether. It is readily soluble in solutions of alkalis. Folic acid is stable in neutral or alkaline solution but its stability decreases as the pH is reduced below 6. Considerable destruction of Folic Acid occurs below pH 4.

ACTIONS: Folic Acid is an important growth factor for a large variety of animal, plant, and microbial cells. Its function in the form of its active metabolite, tetrahydrofolic acid, is to transfer one-carbon molecular fragments such as formyl hydroxymethyl or methyl from one carbon to another. These fragments serve as building units in the synthesis of certain purines, pyrimidines, and amino acids. The methylation of deoxyuridine to thymidine is one of the more important reactions in which Folic Acid participates, this being a preliminary step in the synthesis of desoxyriboneucleic acid (DNA). Deficiency in the synthesis of DNA may interfere with mitosis and be responsible for the gigantic cells (megaloblasts) that are characteristic of megaloblastic anemias. Other important reactions requiring Folic Acid are the metabolic degradation of histidine to glutamic acid and the conversion of serine to glycine.

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 non-tropical 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.

Usual therapeutic dosage: In adults: 0.25 mg. to 1.0 mg. daily. In children (regardless of age); 0.25 mg. 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, nemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance dose should be at least doubled.

HOW SUPPLIED: Compressed, scored 1.0 mg. tablets in bottles of 1000.

Date of Issue October 31, 1972

FOLIC ACID TABLETS
U. S. P. 1.0 mg.

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Manufactured By
BOLAR PHARMACEUTICAL CO., INC.
COPIAGUE, N.Y. 11726

APPROVED

See Accompanying Brochure For Complete Prescribing Information.

Each tablet contains:
Folic Acid USP ..... 1.0 mg.

USUAL DOSE: See accompanying brochure.

FOLIC ACID TABLETS
U. S. P.
1.0 mg.

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Manufactured By
BOLAR PHARMACEUTICAL CO., INC.
COPIAGUE, N.Y. 11726

APPROVED
FEB 15 1973

SEE ACCOMPANYING BROCHURE FOR COMPLETE PRESCRIBING INFORMATION

Each tablet contains:
Folic Acid USP ..... 1.0 mg.

USUAL DOSE: See accompanying brochure.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-141

CSO LABELING REVIEW(S)

REVIEW OF FPL

DATE COMPEETED: 1-10-73

anda 3; 83-141

F.R. DATE: 4-9-71

CO. NAME: Bolar Pharmaceutical Co., Inc.
130 Lincoln Street
Copiague, N.Y. 11726

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

DATE OF SUBMISSION: 12-15-72

TYPE OF SUBMISSION: FPL

CLINICAL EVALUATION:

Review of Labeling: Container labels and insert approvable.

CONCLUSION: Approvable FPL.

RECOMMENDATIONS: Approve FPL, request explanation of discrepancy in marketing quantities; insert restricts availability to containers of 1,000; there are two container labels, one for 100, the other for 1,000.

John H. Eilert, M.D.

John H. Eilert, M.D.

cc:
Dup
BD-69
John H. Eilert, M.D./kim/1-11-73

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-141

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 4-9-71

NDA Number: 83-141

Name and Address of Applicant (City and State)
Bolar Pharmaceutical Company, Inc.
130 Lincoln Steeet
Copiague, New York 11726

Original ____

Amendment 12-15-72

Supplement ____

Other ____

Name of Drug

Nonproprietary Name: Folic Acid

Purpose of Supplement: FPL

Date(s) of Submission(s)

Pharmacological Category: Vitamin

How Dispensed: R_x [X] O.T.C. [ ]

AF Number 10-156

Dosage Form(s): Tablet

Potency (ies): 1 mg.

Related IND/NDA/MF

Satisfactory [ ] Labeling
Date Due Satisfactory (JHEilert)

Satisfactory [ ] Components, Composition, Manufacturing and Controls
Date Due Satisfactpry Active ingredient and drug dosage form copplies with USP specs.

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

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

Establishment Inspection
Satisfactory 2-26-72

Recalls

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

Remarks: Request the HOW SUPPLIED section include a reference to the 100 tablet contamner.

Conclusions: Approved

RJ Wolters 2-8-73
RJWolters

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 4-9-71

NDA Number: 83-141

Original: —

Amendment: 9-28-72

Supplement:

Other:

Name & Address of Applicant (City & State)

Bolar Pharmaceutical Company, Inc.
130 Lincoln Street
Copiague, New York 11726

Name of Drug:

Nonproprietary Name: **Folic Acid**

Purpose of Supplement: **Draft Labeling**

Date(s) of Submission(s):

Pharmacological Category: **Vitamin**

How Dispensed: R_x [X] O.T.C. [ ]

AF Number: ~~10-186~~

Related NDA & MF:

Dosage Form(s): **Tablet**

Potency (ies): **1.0 mg.**

Satisfactory [ ] Labeling Date Due: **Satisfactory (JHEilert)**

Satisfactory [ ] Components, Composition, Manufacturing and Controls Date Due: **Active ingredient and drug doage form complies with USP specs.**

Satisfactory [ ] Biologic Availability Date Due: **NA**

Is data on current formulation? YES [ ] NO [ ]

Satisfactory [ ] Probably or Possibly Effective Indications (if in labeling) Date Data Due:

Establishment Inspection: **Satisfactory 2-7 to 25 -72**

Recalls:

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

Remarks: **Request FPL**

Conclusions: **Rev w/f**

RJ Woltera 10-20-72
RJWoltera

REVIEWER: SIGNATURE: DATE:

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 4-9-71

NDA Number: 83-141

Original: 7-26-72

Amendment:

Supplement:

Other:

Name & Address of Applicant (City & State)

Bolar Pharmaceutical Company, Inc.
130 Lincoln Street
Copiague, New York 11726

Name of Drug:

Nonproprietary Name: Folic Acid

Purpose of Supplement:

Date(s) of Submission(s):

Pharmacological Category: Vitamin

How Dispensed: R_x [X] O.T.C. [ ]

AF Number: 10-156

Related NDA & MF:

Dosage Form(s): Tablet

Potency (ies): 1 mg.

Satisfactory [ ] Labeling
Date Due: To be revised (JHEilert)

Satisfactory [ ] Components, Composition, Manufacturing and Controls
Date Due: Activr ingredient and drug dosage form complys to USP specs.

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

Satisfactory [ ] Probably or Possibly Effective Indications (if in labeling)
Date Data Due:

Establishment Inspection: 2-7- to 25-72

Recalls:

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

Remarks

Request:
1. Revised labeling per MO's review.
2. Include specs for [redacted].
3. Refer applicant to Part 133.13 for requirements regarding stability.

Conclusions

rev w/f

RJ Wolters 9-21-72

RJWolters

REVIEWER: SIGNATURE: DATE:

REVIEW OF ANDA

DATE COMPLETED: 8-11-72

ANDA #: 83-141

F.R. DATE: 4-9-71

CO. NAME: Bolar Pharm. Co., Inc.
130 Lincoln Street
Copiague, L.I., N.Y. 11726

NAME OF DRUG: Trade:
& Folic Acid 1 mg. Tablets U.S.P., in bottles of 1000
Generic:

DATE OF SUBMISSION: 7-26-72

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies: Chemist to evaluate.

2. Review of Labeling: Container label approvable.

Package insert's DESCRIPTION section is superficial, should be expanded to read: "Folic acid is yellow or yellowish orange, odorless, crystalline powder. It is very slightly soluble in water; insoluble in alcohol, chloroform and ether. It is readily soluble in solutions of alkalis. Folic acid is stable in neutral or alkaline solution but its stability decreases as the pH is reduced below 6. Considerable destruction of folic acid occurs below pH 4." The submitted insert does not contain an ACTIONS section. Submitted ACTIONS section should contain the substance of the following:

"Folic acid is an important growth factor for a large variety of animal, plant and microbial cells. Its function, in the form of its active metabolite tetrahydrofolic acid, is to transfer one-carbon molecular fragments such as formyl, hydroxymethyl or methyl from one carbon to another. These fragments serve as building units in the synthesis of certain purines, pyrimidines, and amino acids. The methylation of deoxyuridine to thymidine is one of the more important reactions in which folic acid participates, this being a preliminary step in the synthesis of desoxyribonucleic acid (DNA). Deficiency in the synthesis of DNA may interfere with mitosis and be responsible for the gigantic cells (megaloblasts) that are characteristic of megaloblastic anemias. Other important reactions requiring folic acid are the metabolic degradation of histidine to glutamic acid and the conversion of serine to glycine."

CONCLUSION:

1. Chemist evaluation required.
2. Acceptable container label.
3. Unacceptable insert.

RECOMMENDATIONS:

1. Review by chemist.
2. Approve container label.
3. Require revision of insert to include recommendations detailed above.

John H. Eilert, M.D.

cc:
Dup
BD-69
JHEilert/rt 8-11-72

REVIEW OF RESUBMISSION

DATE COMPLETED: 10-11-72

ANDA #: 83-141

F.R. DATE: 4-9-71

CO. NAME: Bolar Pharm. Co., Inc.
130 Lincoln Street
Copiague, L.I., N.Y. 11726

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

DATE OF SUBMISSION: 9-28-72

TYPE OF SUBMISSION: Manufacturing data, revision of insert in response to 9-22-72 communications.

CLINICAL EVALUATION:

Review of Studies: For evaluation by chemist.

Review of Labeling:

Package insert: Approvable.

CONCLUSION: 1. Review by chemist required.
2. Acceptable insert.

RECOMMENDATIONS: 1. Review by chemist.
2. Approve insert, request FPL.

John H. Eilert, M.D.

John H. Eilert, M.D.

cc:
Dup
BD-69
JHEilert/wlb/10-11-72

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-141

ADMINISTRATIVE DOCUMENTS

[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 6-333).

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 0.15 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 within 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 5397, 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. 20201.

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).

Orig.

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 83-141

DATE APPROVAL LETTER ISSUED: FEB 15 1973

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
- [X] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA

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 mg.

NAME OF APPLICANT *(Include City and State)*

Bolar Pharmaceutical Company
Copiague, New York 11726

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: R.J. Wolters

DATE:

FORM APPROVED BY

NAME: J.L. Meyer

DATE:

FD FORM 1642 (7/69) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-141

CORRESPONDENCE

Rec. W/F Orig E

RESUBMISSION

NDA ORIG AMENDMENT

FPL

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-MY 1-5454

NDA 83 - 141

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

December 15, 1972

Gentlemen:

In reference to your letter of October 25, 1972 regarding our abbreviated new drug application for Folic Acid 1.0 mg. Tablets, NDA 83 - 141 enclosed please find the following:

1. Final printed labels.

2. Final printed package insert.

Sincerely yours,

BOLAR PHARMACEUTICAL CO., INC.

Robert Shulman

ROBERT SHULMAN, PRESIDENT

RECEIVED 1 COPY
PHOTOSTATS OF
COVER LETTER MADE
FOR DUP. ____ TRIP ____

RECEIVED
DEC 26 1972
BUREAU OF DRUGS

83-141

ABBREVIATED
NEW DRUG APPLICATION

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • (516) MY 1-5454

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

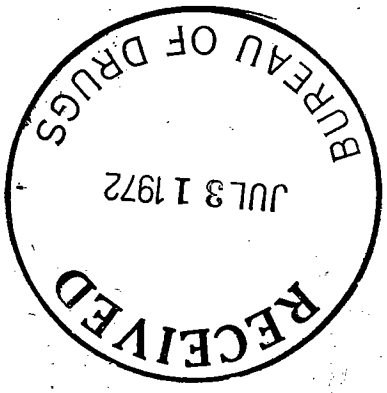
Attention: DESI Project Office

Gentlemen:

This Abbreviated New Drug Application for a compressed tablet of FOLIC ACID 1 mg.
is submitted to meet the conditions specified in regulation 130.4 (f) published in the Federal Register of April 24, 1970 and the DESI announcement on FOLIC ACID 1 MG. TABLETS appearing in the Federal Register of April 9, 1971

Enclosed is a signed form 356H.

APPEARS THIS WAY
ON ORIGINAL



Rev. w/E RESUBMISSION
NDA ORIG AMENDMENT

ORIG

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-MY 1-5454

BUREAU OF DRUGS
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

SEPTEMBER 28, 1972

Gentlemen:

In response to your letter of September 22, 1972 regarding our submitted abbreviated new drug application for Folic Acid 1 mg. Tablets NDA 83-141 please be advised of the following:

Items No. 1, 2, &3 - Three copies of revised Package Insert.
Specifications of the component ———
Statement regarding Stability Studies.

Sincerely yours,
BOLAR PHARMACEUTICAL CO., INC.

Robert Shulman
ROBERT SHULMAN, PRESIDENT

RECEIVED 1 COPY
PHOTOSTATS MADE
FOR DUP_____TRIP_____

RECEIVED
OCT 5 1972
BUREAU OF DRUGS

278-5

NDA 83-141
AP 10-156

OCT 25 1972

Solar Pharmaceutical Company, Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, New York 11726

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.

Reference is also made to your communication dated September 28, 1972, enclosing draft labeling and manufacturing information.

We have completed the review of this abbreviated new drug application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy.

Please submit twelve copies of the printed labels and labeling.

Sincerely yours,

Paul A. Bryan M.D. 10/25/72

Paul A. Bryan, M.D.
Director
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
NYK&DO
Dup
BD-69
BD-66
BD-106
BD-242
BD-100
BD-310
JHEilert/JLMeyer/RJWolters/10-19-72
R/D init. by MClark/JMeyer/10-19-72
Final typing/kim/10-20-72
Approvable.

JHEilert 10-24-72

RJ Wolters 10/24/72
JLMeyer 10/24/72
M Serfe 10/25/72

NDA 83-141
AF 10-156

SEP 22 1972

Solar Pharmaceutical Company, Inc.
Attention: Mr. Robert A. Shulman
130 Lincoln Street
Copiague, New York 11726

Gentlemen:

Reference is made to your abbreviated new drug application dated July 26, 1972, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Tablets, 1 mg.

We have completed the review of this abbreviated new drug application and have the following comments regarding the proposed labeling:

Package Insert:

1. Expand the DESCRIPTION section to read:
"Folic Acid is a yellow or yellowish orange, odorless, crystalline powder. It is very slightly soluble in water; insoluble in alcohol, chloroform and ether. It is readily soluble in solutions of alkalis. Folic acid is stable in neutral or alkaline solution but its stability decreases as the pH is reduced below 6. Considerable destruction of folic acid occurs below pH 4."

2. The ACTION section should include the following:
"Folic Acid is an important growth factor for a large variety of animal, plant, and microbial cells. Its function, in the form of its active metabolite, tetrahydrofolic acid, is to transfer one-carbon molecular fragments such as formyl, hydroxymethyl or methyl from one carbon to another. These fragments serve as building units in the synthesis of certain purines, pyrimidines, and amino acids. The methylation of deoxyuridine to thymidine is one of the more important reactions in which folic acid participates, this being a preliminary step in the synthesis of deoxyribonucleic acid (DNA). Deficiency in the synthesis of DNA may interfere with mitosis and be responsible for the gigantic cells (megaloblasts) that are characteristic of megaloblastic anemias. Other important reactions requiring folic acid are the metabolic degradation of histidine to glutamic acid and the conversion of serine to glycine."

3. It is recommended that the HOW SUPPLIED section include the potency of the drug.

Other information required by Section 130.4(f) of the regulations:

Submit the specifications applied to the component ———

Regarding stability, it is noted that Part 133.13 (21 CFR) of the regulations defines the responsibilities for stability testing.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 9/22/72

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

cc:
NYK-DO
Dup
BD-69
BD-66
BD-106
BD-242
JHEilert/JLMeyer/RJWolters 9-14-72
R/D init. MClark/JLMeyer/9-15-72
Final typing/rt 9-18-72
rev w/f

M. Clark MD for Dr. Eilert 9/21/72
RJ Wolters 9-20-72
JLMeyer 9/21/72

NDA 83-141
AF 10-156

AUG 2 1972

Solar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, New York 11726

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: July 26, 1972

DATE of RECEIPT: July 31, 1972

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,

Marvin Seife 8/1/72

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

cc:
NYK-DO
Dup
BD-69
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BD-106
BD-310
JLMeyer/kim/8-1-72
Ack.

M. Clark MD 8/1/72