

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

85-753

Generic Name: Liothyronine Sodium Tablets, 50mcg

Sponsor: Bolar Pharmaceuticals Co., Inc.

Approval Date: February 3, 1982

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-753

CONTENTS

Reviews / Information Included in this ANDA Review.

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

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

85-753

APPROVAL LETTER

FEB 3 1982

Bolar Pharmaceutical Co., Inc.
Attention: Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application dated April 13, 1977 submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 50 mcg.

We acknowledge receipt of your communications dated November 11, 1981, December 7, 1981, January 21, 1982 and January 22, 1982.

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.

Since the analytical methods have not been validated by our laboratories, this Administration expects you to work to resolve any technical issues which may result with regard to these methods.

In addition, in the absence of sensitive, discriminating assay methodology for the active ingredient, the in vitro dissolution testing requirement for sodium liothyronine may be deferred until adequate assay methodology becomes available.

Any significant

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.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFD-170).

For Subsequent Campaigns: We call your attention to regulation 21 CFR 310.300(b)(3) which requires that all material for any subsequent advertising or promotional campaigns at the time of their initial use be submitted to our Division of Drug Advertising and Labeling (HFD-170) with a completed form FD-2253. A copy of Form FD-2253 is enclosed for your convenience.

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

Sincerely yours,

Marvin Seife 2/3/82

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements
Form FD-2253

NYK-DO DUP HFD-530

HFD-313 HFD-616 HFD-5

HCZell/BTArnwine *B.L. Arnwine HCZell 2/2/82*

R/DinithCZell/MSeife
ft/cj1/2-2-82 approval

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

85-753

FINAL PRINTED LABELING

LIOThYRONINE SODIUM

2/11/82
P. J. C.

DESCRIPTION: Liothyronine Sodium contains liothyronine (L-triiodothyronine or T_3) as the sodium salt. 25 mcg of liothyronine is equivalent to approximately 1 grain of desiccated thyroid or thyroglobulin and 0.1 mg of L-thyroxine.

ACTIONS: Liothyronine Sodium is a synthetic form of a natural thyroid hormone, with all pharmacologic activities of the natural substance. Thyroid hormone acts to promote the synthesis of protein. It increases the metabolic rate of the body, presumably by, among other things, increasing oxygen consumption, altering enzymes (particularly those that affect growth), and altering the permeability of the mitochondrial membranes of cells.

Since liothyronine sodium is not firmly bound to serum protein, it is readily available to body tissues. Following oral administration, about 85% of the dose is absorbed from the gastrointestinal tract. The onset of activity of liothyronine sodium is rapid, occurring within a few hours. Maximum pharmacologic response occurs within two or three days, providing early clinical response. The biological half-life is about 2 1/2 days. The drug has a rapid cutoff of activity which permits quick dosage adjustment and facilitates control of the effects of overdosage, should they occur.

Liothyronine sodium can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

INDICATIONS: Liothyronine sodium, is indicated for thyroid replacement or supplementation in patients with inadequate endogenous thyroid hormone production. These include:

- a) HYPOTHYROIDISM, all gradations from frank myxedema to mild hypofunction; cretinism.
- b) SIMPLE (NON-TOXIC) GOITER, liothyronine sodium may be tried therapeutically in an attempt to reduce the size of such a goiter.

Liothyronine sodium may be used in the T_3 suppression test to differentiate suspected hyperthyroidism from euthyroidism. (See special instructions under Dosage and Administration).

CONTRAINDICATION: Uncorrected adrenal insufficiency.

WARNINGS:

Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Liothyronine sodium should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. In such cases it should be used with caution and initiated at a low dosage, with due consideration for its relatively rapid onset of action. Starting dosage is 5 mcg daily, and should be increased by no more than 5 mcg increments at two-week intervals.

Morphologic hypogonadism and nephrosis should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid; dosage should be started at a very low level and increased gradually.

Severe and prolonged hypothyroidism can lead to a decreased level of adrenocortical activity commensurate with the lowered metabolic state. When thyroid-replacement therapy is administered, the metabolism increases at a greater rate than adrenocortical activity. This can precipitate adrenocortical insufficiency. Therefore, in severe and prolonged hypothyroidism, supplemental adrenocortical steroids may be necessary.

In rare instances the administration of thyroid hormone may precipitate a hyperthyroid state or may aggravate existing hyperthyroidism.

PRECAUTIONS: Since liothyronine sodium is not as firmly bound to serum protein as thyroxine, the PBI usually remains at levels below normal during full replacement therapy using liothyronine sodium.

2/11/82
Brenda J. Cummings

APPROVED

FEB 3 1982

As with all thyroid preparations, thyroid gland function reflected by ^{131}I thyroid uptake may be depressed by liothyronine sodium, particularly when dosage exceeds 75 mcg daily. This effect disappears rapidly, and useful thyroid uptake values may be obtained usually within two weeks following discontinuance of the drug.

ADVERSE REACTIONS: Overdosage will produce signs and symptoms of hyperthyroidism, such as nervousness, cardiac arrhythmias, angina pectoris, and menstrual irregularities. (See OVERDOSAGE section) Medication should be interrupted until symptoms disappear, then resumed in smaller doses. Therapy can usually be resumed after one or two days.

In rare instances, allergic skin reactions have been reported.

DOSE AND ADMINISTRATION: Optimum dosage is usually determined by the patient's clinical response: Confirmatory tests include; Radioactive Iodine T, Resin Uptake, BMR, Thyro Binding Index (TBI), and the Achilles Tendon Reflex Test.

Once-a-day dosage is recommended; although liothyronine sodium has a rapid cutoff, its metabolic effects persist for a few days following discontinuance.

MILD HYPOTHYROIDISM: Recommended starting dosage is 25 mcg daily. Daily dosage then may be increased by 12.5 or 25 mcg every one or two weeks. Usual maintenance dose is 25 - 75 mcg daily. Smaller doses may be fully effective in some patients, while dosage of 100 mcg daily may be required in others.

MYXEDEMA: Recommended starting dosage is 5 mcg daily. This may be increased by 5 to 10 mcg daily every one or two weeks. When 25 mcg daily is reached, dosage may often be increased by 12.5 or 25 mcg every one or two weeks. Usual maintenance dose is 50 to 100 mcg daily.

CRETINISM: Since the mother provides little or no thyroid hormone to the fetus, infants with thyroid dysfunction will require replacement therapy from birth. Treatment should be initiated as early as possible to avoid permanent physical and mental changes.

Recommended starting dosage is 5 mcg daily, with a 5 mcg increment every three to four days until the desired response is achieved. Infants a few months old may require only 20 mcg daily maintenance. At 1 year 50 mcg daily may be required. Above 3 years, full adult dosage may be necessary.

SIMPLE (NON-TOXIC) GOITER: Recommended starting dosage is 5 mcg daily. This dosage may be increased by 5 to 10 mcg daily every one or two weeks. When 25 mcg daily is reached, dosage may be increased every week or two by 12.5 or 25 mcg. Usual maintenance dosage is 75 mcg daily.

IN THE ELDERLY OR IN CHILDREN: Therapy should be started with 5 mcg daily and increased only by 5 mcg increments at the recommended intervals.

WHEN SWITCHING A PATIENT TO LIOTHYRONINE SODIUM FROM: thyroid, L-thyroxine or thyroglobulin, discontinue the other medication, initiate liothyronine sodium at a low dosage, and increase gradually according to the patient's response. When selecting a starting dosage, bear in mind that this drug has a rapid onset of action, and that residual effects of the other thyroid preparation may persist for the first several weeks of therapy.

SPECIAL INSTRUCTIONS FOR T₄ SUPPRESSION TEST: When ^{131}I Thyroid Uptake is in the borderline-high range, administer 75 - 100 mcg of liothyronine sodium daily for 7 days, then repeat ^{131}I Thyroid Uptake Test. In the hyperthyroid patient, 24-hour ^{131}I Thyroid Uptake will not be affected significantly. In the euthyroid patient, 24-hour ^{131}I Thyroid Uptake will drop to less than 20%.

OVERDOSAGE: *Symptoms:* Headache, irritability, nervousness, sweating, tachycardia, increased bowel motility, and menstrual irregularities. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may also develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment: In shock, supportive measures and treatment of unrecognized adrenal insufficiency should be considered.

HOW SUPPLIED: In two dosage forms:

25 mcg tablets in bottles of 100 and 1000.
50 mcg tablets in bottles of 100 and 1000.

DATE OF ISSUE: October 23, 1981

Handwritten signature: Pamela J. Lawrence
Date: 2/1/82

APPROVED

FEB 3 1982

NDC 0725-0061-01

**LIOETHYRONINE
SODIUM
50 mcg.**

CAUTION: Federal law prohibits
dispensing without prescription.

100 TABLETS

BOLAR

PHARMACEUTICAL CO., INC.
COPIAGUE, NEW YORK 11726

Each tablet contains
Liothyronine.....50 mcg.
as the sodium salt
DISPENSE IN TIGHT CONTAINER
AS DEFINED IN THE U.S.P.



USUAL DOSE:
SEE ENCLOSED INSERT.

2/1/82

APPROVED

FEB 3 1982

2/1/82
Prudence J. Lawrence

APPROVED

FEB 3 1982

NDC 0725-0061-10

**LIOETHYRONINE
SODIUM
50 mcg.**

CAUTION: Federal law prohibits
dispensing without prescription.

100 TABLETS

BOLAR

PHARMACEUTICAL CO., INC.
COPIAGUE, NEW YORK 11726

Each tablet contains
Liothyronine.....50 mcg.
as the sodium salt
DISPENSE IN TIGHT CONTAINER
AS DEFINED IN THE U.S.P.



USUAL DOSE:
SEE ENCLOSED INSERT.

2/1/82

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

85-753

CHEMISTRY REVIEW(S)

REVIEW OF ANDAS

DATE COMPLETED: 5-2-77

ANDA #s:

85-755 25 mcg
85-753 50 mcg

NAME OF DRUG: Liothyronine Sodium Tablets

DATE OF SUBMISSION: 4-14-77

TYPE OF SUBMISSION: ANDA

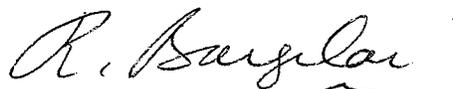
CLINICAL EVALUATION:

1. Review of Studies: EIAR - for review by assigned chemist
Bio studies - deferred
2. Review of Labeling:
 - a) Container labels: Acceptable draft copies of labels for containers of 100 and 1000's in three strengths.
 - b) Package insert: Acceptable drafts for three strengths.

CONCLUSION: Acceptable draft labeling.

RECOMMENDATIONS:

1. Needs chemist's review.
2. Request FPL as per submitted drafts.


R. Barzilai, M.D.

cc:dup
REB/wlb/5-3-77

ABBRI TED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

AF Number 85-753

Name and Address of Applicant (City and State)

Dolar pharmaceutical CO., Inc
Cortland, NY

Original _____
Amendment _____
Supplement _____
Resubmission _____
Correspondance _____
Report _____
Other _____

Purpose of Amendment/Supplement

orig abn NDA

Date(s) of Submission(s)

4/ 177

Pharmacological Category

thyroid
hormone

Name of Drug

liothyronine sodium

Dosage Form(s)

oral

Potency(ies)

25 mcg

How Dispensed

Rx
xxx
OTC

Packaging/Sterilization

requested

Samples

requested

Related IND/NDA/MF

85-755-50 mcg

Labeling

as per MQ(rbarzilaf)

Biologic Availability

in vivo/in vitro requirement currently deferred
as per HFD-500 list dated 3/11/77

Establishment Inspection

requested

Components, Composition, Manufacturing and Controls

as per letter to issue

Remarks

rev w/f

gm11ar

and 4/2/77

APPEARS THIS WAY
ON ORIGINAL

Division

REVIEWER

DATE

ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Statement Date

AF Number 85-753

Name and Address of Applicant (City and State)

Pharmaceutical CO., Inc

Original _____
Amendment _____
Supplement _____
Resubmission _____
Correspondance _____
Report _____
Other _____

Purpose of Amendment/Supplement

amend

Date(s) of Submission:

11/13/77
7/26/77

Pharmacological Category

antibiotic

Name of Drug

Hydrocortisone sodium

Dosage Form(s)

tablet

Potency(ies)

50 mcg

How Dispensed

Rx
OTC

Packaging/Sterilization

required

Samples

required

Related IND/NDA/ME

85-755-50 mcg

Labeling

as per (enclosure)

Biologic Availability

In vivo/in vitro requirement currently deferred
as per FDA DC list dated 3/11/77

Establishment Inspection

required

Components, Composition, Manufacturing and Controls

as per letter to FDA

Remarks

rev u/f

10/11/77
dcl 10/6/77

APPEARS THIS WAY
ON ORIGINAL

Conclusion

REVIEWER

DATE

FROM:

gerry millar

(thru J.L. Meyer)

HFD-530

TO: Mr. David H. Bryant, Office of Compliance

DIVISION

HFD-322

SUBJECT: Inspection Request

SUMMARY

In connection with ANDA -

85-753

85-755

for:

Liothyronine sodium tablets

Applicant:

**Dolar pharmaceutical co., inc
Copiague, NY 11726**

AF -

REQUESTED:

1. Evaluation of compliance with CGMP for:

a. The applicant

b. Others a inspection, as below

2. Recommendation for approval/disapproval of the application/
communication/supplement, based on your evaluation of compliance
with CGMP



REMARKS:

CC: R McDermid HFD 120

SIGNATURE

DOCUMENT NUMBER

ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Statement Date

AF Number 85-753

Name and Address of Applicant (City and State)

Pharmaceutical Co., Inc.

Original _____
Amendment _____
Supplement _____
Resubmission _____
Correspondence Report _____
Other _____

Purpose of Amendment/Supplement

amendment

Date(s) of Submission

11/13/77
7/26/77 + 9/6/77

Pharmacological Category

Name of Drug

anti
hypertensive

hydrochloride sodium

Dosage Form(s)

Potency(ies)

tablets

50 mg.

How Dispensed

Rx
OTC

Packaging/Sterilization

Samples

requested

requested

Related IND/IDA/IF

85-755-50 mg

Labeling

as per (Pharzilaf)

Biologic Availability

in vivo/in vitro requirement currently deferred
as per FDA letter dated 2/11/77

Establishment Inspection

Components, Composition, Manufacturing and Controls

as per letter to FDA

Remarks

rev 1/77

all 11/6/77

APPEARS THIS WAY
ON ORIGINAL

Conclusion

REVIEWER

DATE

CHEMIST'S REVIEW <i>(If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)</i>		1. ORGANIZATION	2. NDA NUMBER 85-753
3. NAME AND ADDRESS OF APPLICANT (City and State) Bolar Pharmaceutical Co. Inc. Copiague, LI, NY 11726		4. AF NUMBER	5. SUPPLEMENT (S) NUMBER(S) DATE(S)
6. NAME OF DRUG Sodium <u>Liothyronine</u>	7. NONPROPRIETARY NAME		9. AMENDMENTS AND OTHER (Reports, etc.) DATES 8/7/80
8. SUPPLEMENT(S) PROVIDES FOR: submission of additional control information and bioavailability & information			
10. PHARMACOLOGICAL CATEGORY thyroid hormone	11. HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC		12. RELATED IND/NDA/DMF(S) 85-755- 25 mcg. Cytomel Tablets Smith, Kline & French Labs. 10-379
13. DOSAGE FORM (S) tablet	14. POTENCY (see) 50 mcg		
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT <input type="checkbox"/> YES <input type="checkbox"/> NO REVIEWED <input type="checkbox"/> YES <input type="checkbox"/> NO	
17. COMMENTS Pending: an approved bioavailability study satisfactory analysis of samples			
18. CONCLUSIONS AND RECOMMENDATIONS Requested: Update application as per tests and specifications / current compendia submit samples for analysis rev w/f			
19. REVIEWER			
NAME J.M. Ross	SIGNATURE <i>J.M. Ross</i>		DATE COMPLETED 9/26/80
DISTRIBUTION	<input type="checkbox"/> ORIGINAL JACKET	<input type="checkbox"/> REVIEWER	<input type="checkbox"/> DIVISION FILE

Enter evaluation or comments for each item. If necessary, continue on 8" x 10 1/2" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.

20. COMPONENTS AND COMPOSITION (6, 7)

see application

21. FACILITIES AND PERSONNEL (8a,b)

22. SYNTHESIS (8c)

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

is tested as per USP
Requested: update tests and specifications as per current USP

b. OTHER INGREDIENTS

are tested as per USP/NF
Requested: update tests and specifications

24. OTHER FIRM(s) (8l)

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

26. CONTAINER (8j)

opaque white high density polyethylene containers

27. PACKAGING AND LABELING (8l,m)

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

is tested as per USP..... Requested: update tests and specifications

29. STABILITY (8p)

protocol submitted and some challenge studies

30. CONTROL NUMBERS (8c)

31. SAMPLES AND RESULTS (9)

a. VALIDATION

requested

b. MARKET PACKAGE

32. LABELING (4)

Satisfactory(RBarzilai)

33. ESTABLISHMENT INSPECTION

Bolar Pharmaceutical Co. Inc.

incompliance

7/31./79

34. RECALLS

CHEMIST'S REVIEW FOR
ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Statement Date:

NDA # 85-753

NAME AND ADDRESS OF APPLICANT:

Bolar Pharmaceutical Co., Inc.
Copiague, New York 11726

ORIGINAL 4-8-77
AMENDMENT 11-4-81, 12-7-81
SUPPLEMENT 1-21-82, 1-22-82
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

DATE(s) of SUBMISSION(s)

PHARMACOLOGICAL CATEGORY
Thyroid hormone

NAME OF DRUG

Liothyronine Sodium

HOW DISPENSED

RX xx OTC

DOSAGE FORM

tablets

POTENCY(IES)

50 mcg

RELATED IND/NDA/DMF

85-755

STERILIZATION

NA

SAMPLES

To be sent for methods
validation

LABELING

Satisfactory as per MS 1/22/82

BIOLOGIC AVAILABILITY Bioavailability study although a Federal Register requirement (FR, Vol 42, No. 232, Dec. 2, 1977) has been waived because an acceptable study was done on lower dosage strength. However dissolution requirement has not been met because of

ESTABLISHMENT INSPECTION lack of a workable method. Firm must make a commitment to perform dissolution when method is available.

Satisfactory as per alert list.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Satisfactory. Updated excipient specs for current compendia. An method for content uniformity and assay for active ingredient and finished dosage form.

PACKAGING

STABILITY: Satisfactory. Updated room temperature stability data are sufficient.
Protocol: for requested 3 yr exp. dating. Also 3 mos stability data submitted at challenge conditions.

Exp. Date: 36 mos.

REMARKS & CONCLUSION: Approved BTArnwine

Pamela J. Arnwine 2/2/82
HC Zell 2/2/82

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

85-753

**BIOEQUIVALENCE
REVIEW(S)**

Liothyronine Sodium
Tablets, 25 and 50 mcg
ANDA 85-755
ANDA 85-753

Bolar Pharmaceutical Co., Inc.
Copiague, New York
Submissions Dated:
October 12, 1981
November 4, 1981

REVIEW OF CORRESPONDENCE

Bolar conducted an acceptable bioequivalence study comparing its liothyronine sodium tablets, 25mcg (lot #083269) to Cytomel 25mcg tablets (lot #550016) manufactured by Smith, Kline and French.

With respect to dissolution testing, the firm was advised that the Laboratory Branch (HFD-524) is developing a methodology for dissolution testing of liothyronine sodium tablets. When the methodology becomes available the firm would be expected to undertake dissolution testing of its products in comparison with Cytomel using the new methodology.

The purpose of this communication (Bolar letters to Dr. Seife dated October 12 and November 4, 1981; see attachments) was to advise the Agency that:

"Bolar will undertake dissolution testing of its liothyronine sodium drug product(s) in comparison to Smith, Kline and French Company's Cytomel, 25 (and 50)mcg tablets(s), using the new methodology when it become available."

COMMENTS:

1. The Division (HFD-520) received —, liothyronine tablets, 25mcg (lot #061073) from Bolar on October 24, 1981.
2. I called Mr. Jack Rivers (Bolar) to inform him that the development of dissolution test methodology was running behind schedule; the method should be ready in about 6 months. I also asked Mr. Rivers to send a sample (200 tablets) of the liothyronine sodium tablets, 25 and 50mcg for HFD-524 to use in methodology development. I specifically requested some samples of lot #083269 which was use in the in vivo bioavailability study.
3. Samples — tablets) of liothyronine sodium tablets, 25 and 50mcg should be forwarded to:

Ms. Ting E. O. Chen (Chemist)
Food and Drug Administration (HFD-522)
Room 16B-08
5600 Fishers Lane
Rockville, MD 20857

RECOMMENDATION:

The firm's commitment to do dissolution testing, when methodology becomes available, is acceptable.

From a biopharmaceutical point of view the applications for liothyronine sodium tablets, 25 and 50mcg-strength are approvable.

The above recommendations above as well as comments (#2 and 3) should be forwarded to the firm.

Francis R. Pelsor 1/6/82
Francis R. Pelsor, Pharm. D.
Biopharmaceutics Review Branch

cc: ANDA 85-755 orig., ANDA 85-753, HFD-530(4), HFD-522(Pelsor, Ise),
Chron File, Drug File, Review File, HFD-503(Mr. Hare)

FRPELSOR/mk/12/23/81 (8036E)
FRP/mrs/1/6/82 FT

RD INITIALED BY CMISE
FT INITIALED BY CMISE *C. M. Se 1-7-82*

CONCUR: *Bernard E. Cabana* Date *1/19/82*
Bernard E. Cabana, Ph.D.
Director, Division of Biopharmaceutics

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**CENTER FOR DRUG
EVALUATION AND
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APPLICATION NUMBER:

85-753

**ADMINISTRATIVE
DOCUMENTS**

NOTICE OF APPROVAL NEW DRUG APPLICATION OR SUPPLEMENT		NDA NUMBER 85-753 DATE APPROVAL LETTER ISSUED FEB 3 1982
TO: Press Relations Staff (HFI-40)	FROM: <input checked="" type="checkbox"/> Bureau of Drugs <input type="checkbox"/> 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 APPLICAT O.: <input type="checkbox"/> ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO NDA <input checked="" type="checkbox"/> ABBREVIATED ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO ANDA	CATEGORY <input checked="" type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY	
TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG. Liothyronine Sodium		
DOSAGE FORM tablets	HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> 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.) Liothyronine Sodium, 50 mcg : :		
NAME OF APPLICANT (Include City and State) Bolar Pharm. Co., Inc. - 130 Lincoln St. - Copiague, NY 11726		
PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY Thyroid hormone.		
COMPLETE FOR VETERINARY ONLY		
ANIMAL SPECIES FOR WHICH APPROVED		
COMPLETE FOR SUPPLEMENT ONLY		
CHANGE APPROVED TO PROVIDE FOR		
APPEARS THIS WAY ON ORIGINAL		
FORM PREPARED BY		
NAME Brenda Arnwine	<i>Brenda J. Arnwine</i>	DATE 2/2/82
FORM APPROVED BY		
NAME HCZell	<i>HCZell</i>	DATE 2/2/82

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE

1/22/82

NDA NUMBER

85-753

IND NUMBER

TELECON/MEETING

INITIATED BY

APPLICANT/
SPONSOR

FDA

MADE

BY TELE-
PHONE

IN PERSON

PRODUCT NAME

Lithyponine
Sodium Table
50mcg

FIRM NAME

Balan Pharma-
ceutical

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD

Jack Ruess

TELEPHONE NO.

I called Jack Ruess to tell him that we needed some fresh stability data for the subject drug product. The stability data in the application was submitted in 1977 ~~for~~ covering 36 months. He said he would send challenge condition data and room temperature stability data

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE

Brenda J. Annune

DIVISION

BDM

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 9/23
FROM: J. M. Ross	OFFICE:	
TO:	DIVISION	
SUBJECT: Review of Bioavailability Studies		
SUMMARY 85-753 + 85-755 Sodium Liothyronine Tabs. Bolar. Pharm. Co. Inc.		
<p>In a conversation today (9/23/80) with Dr. Isci, I was told that so far their bio-studies are not satisfactory. In fact they have been in touch with Bolar representatives recently. Bolar's representatives were to send their studies to Harvard Univ for a second opinion. As of yet our Div. of Pharm. has received no reply from Bolar concerning this.</p> <p>Presently Dr. Isci indicated that based on the information we have, the study will not be approved.</p>		
SIGNATURE <i>J. M. Ross</i>	DOCUMENT NUMBER 85-755/752	

MEMORANDUM

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

TO : Director
Division of Generic Drug Monographs (HFD-530)
Attn: G. Millar

DATE: July 31, 1979

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

SUBJECT: / Approvable ANDAs - 85-753 - Liothyronine Sodium Tablets
85-755 - Liothyronine Sodium Tablets

APPLICANT: ✓ Bolar Pharmaceutical Co., Inc.,
Copiague, New York.

~~_____~~
~~_____~~
~~_____~~

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

Our evaluation is based in part on an inspection conducted November 29, 30, 1977.

David H. Bryant
David H. Bryant

cc: NYK-DO (HFR-2100)
HFD-322 Firm File
HFD-300 R/F
HFD-530 (2)
HFD-530 (ANDA Orig)

WSKlatch: fjh: 7/31/79

WSKlatch 7/31/79

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

85-753

CORRESPONDENCE

FEB 1 1982

NDA ~~85-753~~
NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your correspondence dated October 20, 1981 and November 4, 1981 regarding Liothyronine Sodium Tablets, 25 and 50 mcg.

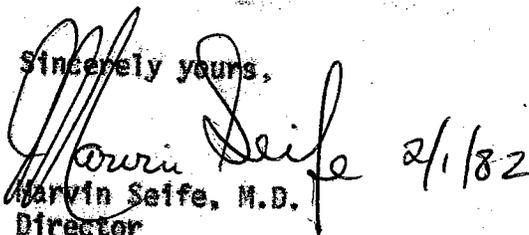
The letter was reviewed by our Division of Biopharmaceutics and they have the following comments:

- "1. Mr. Jack Rivers (Bolar) was informed that the development of dissolution test methodology was running behind schedule; the method should be ready in about 6 months. Mr. Rivers was asked to send a sample (—tablets) of the liothyronine sodium tablets, 25 and 50 mcg for HFD-524 to use in methodology development. Samples of lot #083269 which was used in the in vivo bioavailability study were specifically requested.
2. Samples (—tablets) of liothyronine sodium tablets, 25 and 50 mcg should be forwarded to:

Ms. Ting E.O. Chen
FDA/Division of Biopharmaceutics (HFD-522)
5600 Fishers Lane
Rockville, MD 20857

RECOMMENDATIONS: The firm's commitment to do dissolution testing, when methodology becomes available, is acceptable."

Sincerely yours,


Marvin Seife, M.D.

Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO DUP
HFD-530
HFD-520
MSeife/wh/2-1-82
bio



SOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

January 22, 1982

NDA # 85-753

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

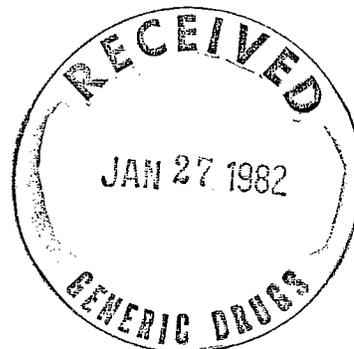
In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg enclosed please find room temperature stability data.

Sincerely,

Robert Shulman, President

ENCL:

RS/mes





SOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

January 21, 1982

NDA # 85-753

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

*Received
NDA # 85-753
1/21/82*

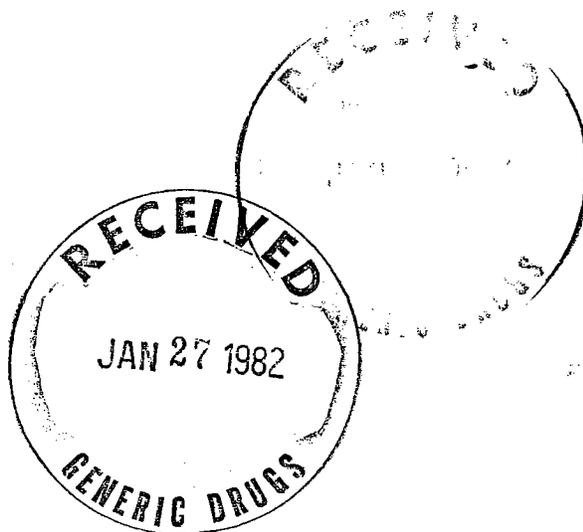
ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg enclosed please find challenge condition stability data.

Sincerely,


Robert Shulman, President



Orig



BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

December 7, 1981

NDA # 85-753

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg, enclosed please find the following _____ specifications.

1. _____ (to replace the _____ Specifications previously sent)
2. _____

Sincerely,

Robert Shulman, President

ENCLS:
RS/fn





BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

1/22/82
THE SUBMITTED FPL IS SATISFACTORY.
m.s.

November 4, 1981

NDA # 85-753

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg and your letter of September 29, 1980, please be advised of the following:

1. Current Final Printed Inserts and Labels are enclosed.
2. A revised raw material specification for Liothyronine Sodium is enclosed. The enclosed method is an ~~_____~~ analysis developed by our Analytical Research and Development Section under the Direction of Ms. Gena Finelli. It was ascertained that the USP assay for Liothyronine is based upon total iodine content and therefore is not specific for Liothyronine. The enclosed ~~_____~~ analysis allows for specific quantitation of Liothyronine as well as Diiodothyronine and Thyroxine.
3. Revised excipient specifications in accord with current compendia requirements are enclosed.
4. Finished dosage form specifications including Content Uniformity and Stability Testing Procedures along with Precision and Recovery Data are enclosed.

NDA ORIG AMENDMENT

BIOAVAILABILITY MATERIAL **FPU**





BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

NDA # 85-753 (CON'T)

5. Samples of the dosage form along with analytical results of all tests performed are enclosed.

Samples of the active ingredient were submitted on September 23, 1981 as part of an amendment to our Liothyronine Sodium Tablets, 25 mcg, NDA # 85-755.

Bolar will undertake dissolution testing of its Liothyronine Sodium drug product in comparison to Smith, Klein and French's Cytomel 50 mcg Tablets, using the new methodology when it becomes available.

Sincerely,

Robert Shulman, President

ENCLS:

RS/fn

SEP 29 1980

NDA 85-753

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, L.I. NY 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 Sodium Liothyronine Tablets, 50 mcg.

We acknowledge receipt of your communication dated August 7, 1979 enclosing additional control information.

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

1. Appropriately update your application as to tests and specifications for the active ingredient, _____ and finished dosage form per current compendium.
2. Submit samples of the active ingredient and finished dosage form with the analytical results of all tests performed for the lot submitted.

We call to your attention that your bioavailability studies are under review by our Division of Biopharmaceutics and a reply will be issued when commented upon.

Please submit the above information promptly.

NYK-DO DUP HFD-614
JLMeyer/JMRoss
R/DinitJMeyer/MSeife
ft/cjl/9-25-80 rev w/f

JMeyer 9/26/80

Sincerely yours,

Marvin Seife 9/29/80
Marvin Seife, M.D.
Director

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

JMeyer 9/26/80

Drug

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

August 7, 1979

NDA # 85-753

NDA ORIG AMENDMENT

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg., enclosed please find the following:

1. Samples of the drug dosage form.
2. Updated production order.
3. Analytical results of the drug dosage form.
4. Challenge condition stability data for lot number 059062.
5. Stability protocol and revised reporting format.

We are currently developing an ~~new~~ procedure to test for potency and dissolution on the finished dosage form. As soon as available the analytical method and results will be forwarded to you.

We will submit analytical results of the first several batches manufactured.

Based upon the enclosed challenge condition data we are requesting a two year expiration date.

Sincerely,

Robert Shulman

Robert Shulman, President

ENCLS:
RS/fn



al law prohibits dispensing without prescription."

(b) The drug product is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indication is as follows:

For radiographic visualization of the bronchial tree.

3. *Marketing status.* (a) Marketing of such drug product which is now subject of an approved or effective new drug application may be continued provided that, on or before January 31, 1978, the holder of the application submits, if he has not already done so, (i) a supplement for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) a supplement to provide full updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)).

(b) Approval of an abbreviated new drug application (21 CFR 314.1(f)) must be obtained prior to marketing such products. The applications shall contain full information with respect to items 6 (components), 7 (composition) and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)). Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70).

Dated: November 11, 1977.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc. 77-34268 Filed 12-1-77; 8:45 am]

[4110-03]

[Docket No. 76N-0451; DESI 2245]

SODIUM LIOTHYRONINE

Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice sets forth the conditions for marketing sodium liothyronine tablets for the indications for which it continues to be regarded as effective and offers an opportunity for a hearing concerning indications reclassified to lacking substantial evi-

dence of effectiveness. This drug is used for certain conditions of inadequate endogenous thyroid production.

DATES: Hearing requests due on or before January 3, 1978. Supplements due on or before January 31, 1978.

ADDRESSES: Communications forwarded in response to this notice should be identified with reference number DESI 2245, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857.

Supplements (identify with NDA number): Division of Metabolism and Endocrine Drug Products (HFD-130), Room 14B-04, Bureau of Drugs.

Abbreviated new drug applications and notices of claimed investigational exemption for a new drug (IND) (identify as such): Division of Generic Drug Monographs (HFD-530), Bureau of Drugs.

Requests for hearing (identify with Docket number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC-20), Room 4-65.

Requests for the report of the National Academy of Sciences, National Research Council, Public Economics and Documents Center (HFC-18), Room 4-62.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-340), Bureau of Drugs.

FOR FURTHER INFORMATION CONTACT:

John H. Hazard, Jr., Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, (301-443-3650).

SUPPLEMENTARY INFORMATION: In a notice (DESI 2245) published in the FEDERAL REGISTER of September 25, 1969 (34 FR 14775), the Food and Drug Administration announced its conclusions that the drug product described below is (1) effective for certain conditions resulting from inadequate endogenous thyroid production, and (2) possibly effective for gynecological disorders associated with hypothyroidism. In addition, that notice should have stated that the drug product is effective for use in the T₃ suppression test to differentiate suspected hyperthyroidism from euthyroidism. No data in support of the less-than-effective indication were submitted, and it is now reclassified to lacking substantial evidence of effectiveness. This notice offers an opportunity for a hearing concerning that indication and sets forth the conditions for marketing the drug product for the indications for which it is re-

garded as effective. The other drug (thyroglobulin) included in the September 25, 1969, notice is not affected by this notice.

NDA 10-379; Cytomel Tablets containing sodium liothyronine; Smith Kline & French Laboratories, Division of SmithKline Corp., 1500 Spring Garden St., Philadelphia, Pa. 19101.

Such 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. An approved new drug application is a requirement for marketing such drug products.

In addition to the holder of the new drug application specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, that is identical, related, or similar to the drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to the drug product named in this notice by writing to the Division of Drug Labeling Compliance (address given above).

A. *Effectiveness classification.* The Food and Drug Administration has reviewed all available evidence and concludes that the drug is effective for the indications stated in the labeling conditions below. The drug now lacks substantial evidence of effectiveness for the indication evaluated as possibly effective in the September 25, 1969, notice.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* The drug is in tablet form suitable for oral administration.

2. *Labeling conditions.* (a) The label bears the statement, "Caution: Federal law prohibits dispensing without prescription." (b) The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indications are as follows:

(1) Thyroid replacement in patients with inadequate endogenous thyroid hormone production. These include mild hypofunction, cretinism, and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

(2) Simple (nontoxic) goiter. The drug may be used therapeutically in

an attempt to reduce the size of such a goiter.

(3) For use in the T₄ suppression test to differentiate suspected hyperthyroidism from euthyroidism.

3. *Marketing status of approved products.* Marketing of such drugs products that are now the subject of an approved or effective new drug application may be continued provided that, on or before January 31, 1978, the holder of the application submits the following if he has not previously done so: (i) a supplemental for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) a supplement to provide updating information with respect to items 6 (components), 7 (composition), 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)) to the extent required in abbreviated applications (21 CFR 314.1(f)).

4. *Marketing status of all other products.* Approval of an abbreviated new drug application (21 CFR 314.1(f)) must be obtained prior to marketing such drug products. The abbreviated new drug application is required to contain evidence from in vivo studies demonstrating bioequivalence to an appropriate reference standard. Such bioavailability studies shall consist of either single- and/or multiple-dose blood level studies or comparison of acute pharmacological activity to an appropriate reference material. Multiple-dose studies will require prior submission of a Notice of Claimed Investigational Exemption for a New Drug (IND) including a protocol for such studies. Because of inherent toxicological side effects associated with this drug, it is advisable that firms submit a protocol with the ANDA prior to undertaking a single-dose study in human subjects. Abbreviated new drug applications and notices of claimed investigational exemption for a new drug (IND) (identify as such) should be directed to the Division of Generic Drug Monographs (HFD-530), Bureau of Drugs (address given above). Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

C. *Notice of opportunity for hearing.* On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5), demonstrating the effectiveness of the drug(s) for the

indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness. (In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Parts 310, 314), the applicant(s) and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file

(1) on or before January 3, 1978, a written notice of appearance and request for hearing, and (2) on or before January 31, 1978, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegation or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk between the hours of 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053; as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.82).

JAN 24 1978

NDA 85-759

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 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 Liothyronine Sodium Tablets, 50 mcg.

We acknowledge receipt of your communication dated October 24, 1977.

We note the material submitted.

However, the Federal Register notice of December 2, 1977, provides updated guidelines to be included in an abbreviated new drug application.

If you elect to complete this application, the information so requested should be submitted.

Please let us have your response promptly.

Sincerely yours,

for G. Seife 1/23/78

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosure: FR 12-2-77

cc:
NYK-DO
HFD-614
JMeyer/GMillar
R/D init JMeyer/MSeife/1/23/78
ps/1/23/78
rev w/f

che 1/23/78
JMeyer 1/23/78

Rev w/f ORIGINAL

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

October 24, 1977

NDA 85-753

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

RESUBMISSION

NDA ORIG AMENDMENT

ATTN: Dr. Marvin Seife

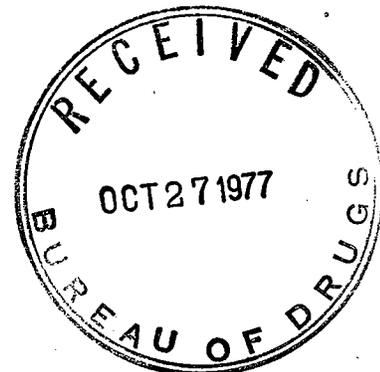
Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg. and your letter of October 11, 1977, please be advised of the following:

- 1) Printed labeling has been previously submitted.
- 2) Regarding stability we are enclosing stability data on a production batch of tablets. Lot # 024741 was manufactured and initially assayed during April of 1974. The samples were kept at room temperature and were packaged in the container/closure system in which they were marketed. The enclosed stability data summary shows 36 month data. We have marketed this product since 1974, discontinuing the sale as a result of the Judge Green decision. The actual analytical work is available if needed.
- 3) Samples have been previously submitted. The submitted samples were from the same batch as those used in the stability study.

Sincerely,


Robert Shulman, President
ENCLS:
RS/fa



NOV 4 1977

NDA 85-753

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 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 Liothyronine Sodium Tablets, 50 mcg.

We acknowledge receipt of your communication dated September 6, 1977, amending the application with copies of printed labeling.

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:

That requested in our letter of October 11, 1977 pertaining to stability and container/closure systems.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 11/4/77
Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:

NYK-DO

HFD-614

BBayzilai/JMeyer/GMillar

R/D init JMeyer/MSeife/11/1/77

ps/11/1/77

rev w/f

JMeyer 11/3/77

ch 11/1/77

AS 11/2/77

Rev W K-
Orig

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

September 6, 1977

NDA 85-753

RESUBMISSION

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

FPLK
Abayilai
10/31/77

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mg and our letter of July 26, 1977, enclosed please find:

- 1) Final Printed package inserts and labels.

Sincerely,

[Signature]
Robert Shulman, President

ENCLS:
RS/fa

RECEIVED
SEP 08 1977
BUREAU OF DRUGS

OCT 11 1977

NBA 85-753

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 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 Liothyronine Sddium Tablets, 50 mcg.

We acknowledge receipt of your communication dated July 26, 1977, amending the application.

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. Printed labeling, as per your commitment.
2. For stability:
 - a) we are requesting a signed statement that you will check the stability of production batches (in the container/closure system in which it is to be marketed); submit results of these studies at 3, 6, 12, 18 and 24 month intervals and yearly thereafter; and promptly withdraw from the market any lots that may become subpotent.
 - b) we are requesting studies at challenge conditions - especially with respect to humidity and cycling.
 - c) we note your proposal for a 24 month expiration date.
3. For processing et al: we are requeusting studies on the effect of _____
4. We are requesting samples and your analytical results.

Please let us have your response promptly.

JLMeyer/GMillar 10-5-77
r/d/ init. JMeyer/10-5-77
f/t/wlb/10-6-77
rev w/f
cc:
NYK-DO
DUP HFD-614

done 10/6/77
JMeyer (10/7/77)

Sincerely yours,

Marvin Seife
Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
10/7/77

Rec'd F
Orin

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

July 26, 1977

NDA 85-753

RESUBMISSION

NDA ORIG AMENDMENT

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife

Dear Dr Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 50 mcg, and your letter of June 21, 1977, enclosed please find the following:

- 1) Certificate of analysis from our supplier.
- 2) Samples and our analytical results.

We will submit analytical results for production batches and lots of active ingredient used.

We are enclosing 36 month stability data for the enclosed sample.

The container closure system as described in our ANDA protects the contents from contamination by extraneous liquids, solids and vapors.

The _____ of the Sodium Liothyronine is _____

We will forward printed package inserts and container labels as soon as available from our printer.

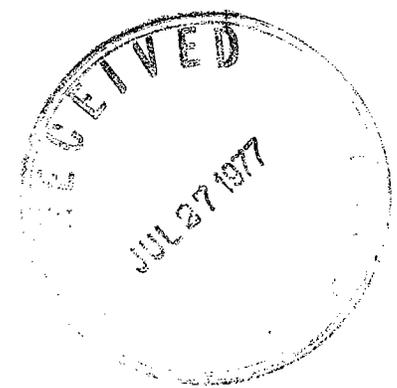
Sincerely,



Robert Shulman, President

ENCLS:

RS/fa



JUN 21 1977

NDA 85-753

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application dated April 13, 1977 submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 50 mcg.

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. For labeling: copies of printed labeling in accord with the submitted drafts (containers and insert).
2. For the active ingredient:
 - a) identification of the actual manufacturer and submission of a certificate of analysis from your _____
 - b) a commitment to submit analytical results for lot used.
3. For the drug dosage form:
 - a) a commitment to submit analytical results for production batches.
 - b) stability data
 - c) demonstration that the container/closures system is suitable for the intended use. Here we call your attention to the USP XIX requirement for "tight" containers.
 - d) samples and your analytical results.

Please let us have your response promptly.

cc: NYK-DO *Barzilai 6/20/77*

HFD-614 HFD-616 *Miller 6/14/77*

RBarzilai/JLMeyer/Miller-6/14/77

R/D init. JMeyer/MSeife/6/20/77

rev w/f *Chubb 6/20/77*

ca/6/20/77

Sincerely yours,

Marvin Seife 6/24/77
Marvin Seife, M.D.

Director

Division of Generic Drug Monographs

Office of Drug Monographs

Bureau of Drugs

NDA 85-753

Bolar Pharmaceutical Company, Inc.
Attention: Robert Shulman
130 Lincoln Street
Copiague, NY 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: Liothyronine Sodium 50 mcg. Tablets

DATE OF APPLICATION: April 13, 1977

DATE OF RECEIPT: April 15, 1977

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, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

NYK-DO

DUP

HFD-614, HFD-616

JLMeyer/cjb/4-26-77

ack

required by law to be approved by the Secretary of Commerce.

04. Subpoenas—a. *Information under the control of the Civil Service Commission.* 1. If a subpoena or other judicial order for information contained in an official personnel folder in the physical custody of the Department is served on an employee of the Department responsible for the folder, he shall disclose such information as is allowed under Part 294 of the Civil Service Regulations (5 CFR 294.101-294.1001). However, he should retain custody of the information and, as necessary, request permission of counsel or the court to furnish a certified copy for inclusion in the court record. (See 5 CFR 294.108(c).)

2. In an unusual situation or a situation in which information not available under Part 294 of the Civil Service Regulations is sought, the Department employee who received the subpoena shall immediately forward it and the official personnel folder containing the information sought to the General Counsel of the Department for transmittal to the General Counsel, U.S. Civil Service Commission, Washington, D.C. 20415. When this is done, the Department employee shall inform the person who applied for the subpoena that the subpoena and the information sought have been sent to the Civil Service Commission pursuant to 5 CFR 294.108(c) (2) and, if necessary, and upon advice of the General Counsel of the Department, request a postponement of the scheduled appearance.*

b. *Other information within the purview of this order.* When a subpoena duces tecum or other legal demand for the production of records or information relating to personnel other than as authorized pursuant to this order is served upon any officer or employee of the Department other than the Secretary, he shall comply with section 7, "Compulsory Process Requesting Documents or Testimony," of Department Order 64, "Public Information."

SEC. *12* Saving provision. This order shall be deemed consistent with Department Order 64. Any other orders or parts of orders or delegations of authority which are inconsistent herewith are hereby superseded.

LARRY A. JOBE,
Assistant Secretary
for Administration.

[F.R. Doc. 69-11430; Filed, Sept. 24, 1969;
8:48 a.m.]

[Dept. Order 5-B, Amdt. 1]

ECONOMIC DEVELOPMENT ADMINISTRATION

Organization and Function¹

SEPTEMBER 10, 1969.

The material appearing at 34 F.R. 6709 of April 19, 1969, is amended as follows: Department Order 5-B of March 17, 1969, is hereby amended as follows:

Organization chart filed as part of the final document.

1. **Sec. 7. Office of Administration and Program Analysis.** Paragraphs .01 and .02 are amended, and a new Paragraph .03 is added, to read:

.01 The *Program Analysis Division* shall develop and implement measures of resource utilization for programming and budgeting purposes, develop and conduct a systematic program evaluation effort for EDA; prepare the annual Program Memorandum and analytical studies required by the Bureau of the Budget; and develop cost benefits studies to aid the Assistant Secretary in making choices and decisions between alternative programs for economic development projects, activities, and programs in achieving the objectives of the Act and EDA.

.02 The *Management Analysis Division* shall: Conduct organization and management studies and surveys; plan and conduct a program for achieving maximum economy, effectiveness, and efficiency, and for obtaining optimum personnel utilization; develop and conduct a program for the efficient management of all official records, including an issuance system for administrative and program orders, and the design and control of official forms; and develop and administer a reports control system for all administrative and operational reports.

.03 The *Budget Division* shall: Develop and manage an integrated financial management and budgeting system for EDA; It shall develop and prepare the annual budget for EDA; be responsible for the total financial program of EDA, and for the fiscal aspects of EDA programs entrusted to other Federal agencies; and operate a fiscal control system for both program and administrative expenses consistent with the requirements of the Anti-Deficiency Act, which shall include but not be restricted to, allotment of funds, operating budgets, employment limitations, and analyses of reports and proposed actions relating thereto.

2. The remaining paragraphs of section 7 are renumbered paragraphs .04 through .08.

LARRY A. JOBE,
Assistant Secretary
for Administration.

[F.R. Doc. 69-11431; Filed, Sept. 24, 1969;
8:48 a.m.]

DEPARTMENT OF AGRICULTURE

Office of the Secretary

WASHINGTON

Designation of Areas for Emergency Loans

For the purpose of making emergency loans pursuant to section 321 of the Consolidated Farmers Home Administration Act of 1961 (7 U.S.C. 1961), it has been determined that in the hereinafter-named counties in the State of Washington, natural disasters have caused a need for agricultural credit not readily available from commercial banks, coopera-

tive lending agencies, or other responsible sources.

WASHINGTON

Chelan,
Douglas.

Ozkanogan.

Pursuant to the authority set forth above, emergency loans will not be made in the above-named counties after June 30, 1970, except to applicants who previously received emergency or special livestock loan assistance and who can qualify under established policies and procedures.

Done at Washington, D.C., this 19th day of September, 1969.

CLIFFORD M. HARDIN,
Secretary of Agriculture.

[F.R. Doc. 69-11427; Filed, Sept. 21, 1969;
8:48 a.m.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 2245]

THYROGLOBULIN AND SODIUM LIOTHYRONINE

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 drugs:

1. Thyroglobulin, marketed as Proloid, 1/4, 1/2, 1, 1 1/2, 3, and 5 grains per tablet by Warner-Chilcott Laboratories, Division of Warner-Lambert Pharmaceutical Co., 201 Tabor Road, Morris Plains, N.J. 07950 (NDA 2-245).

2. Sodium Liothyronine, marketed as Cytocel, 5 and 25 micrograms of base per tablet, by Smith Kline and French Laboratories, 1500 Spring Garden Street, Philadelphia, Pa. 19101 (NDA 10-379).

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.

THYROGLOBULIN; SODIUM LIOTHYRONINE

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

1. Both drugs are effective for certain conditions resulting from inadequate endogenous thyroid production.

2. Thyroglobulin lacks substantial evidence of effectiveness for the recommendation: "therapeutic trial for non-specific symptoms, such as fatigue, depression, frequent colds, and low resistance when pharmacologic effects of a natural metabolic stimulant may be helpful." This claim was not part of any labeling provided for in the "deemed approved" new drug application.

3. Sodium liothyronine is regarded as possibly effective for the labeled indication "gynecological disorders associated with hypothyroidism." This indication should be made more precise with adequate supporting data for each claim of therapeutic effectiveness.)

B. *Form of drug.* Thyroglobulin and sodium liothyronine preparations are in tablet form suitable for oral administration and contain per dosage unit an amount appropriate for administration in the dosage ranges described in the labeling conditions in this announcement.

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 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 forth below.)

THYROGLOBULIN

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should 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 pharmacological/physiological actions of the active ingredient of the drug. When such actions are based on animal studies alone, this should be clearly stated. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

Conditions of inadequate endogenous thyroid production: Eg.
Replacement therapy in cretinism and myxedema.

Replacement therapy will be effective only in manifestations of hypothyroidism.

Simple (nontoxic) goiter, where in non-emergency situations the drug may be tried therapeutically in an attempt to reduce the size of such goiters.

CONTRAINDICATIONS

Uncorrected adrenal insufficiency.

WARNINGS

Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg.) and increasing by the same amount in increments at 2 week intervals. A careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypo-pituitarism is present,

the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

PRECAUTION

As with all thyroid preparations, this drug will alter results of thyroid function tests.

ADVERSE REACTIONS

Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism such as nervousness, cardiac arrhythmias, and angina pectoris.

DOSE AND ADMINISTRATION

Optimal dosage is usually determined by the patient's clinical response. Confirmation tests include BMR, $T_{131}I$ Resin sponge uptake, $T_{131}I$ red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Dosage should be started in small amounts and increased gradually, with increments at 1-2 week intervals. Usual maintenance doses is 0.5 to 3.0 grains (32 to 190 mg.) daily.

OVERDOSAGE

Symptoms: Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

SODIUM LIOTHYRONINE

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should 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 pharmacological/physiological actions of the active ingredients of the drug. When such actions are based on animal studies alone, this should be clearly stated. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

(Use the same indications as are described for thyroglobulin.)

CONTRAINDICATIONS

Uncorrected adrenal insufficiency.

WARNINGS

Sodium liothyronine should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 5 mcg. and increasing by 5 mcg. increments at 2-week intervals.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypo-pituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

PRECAUTIONS

Since liothyronine is not as firmly bound to serum protein as thyroxine, the PBI may remain at hypothyroid levels even though the patient is euthyroid (liothyronine may lower

the PBI when administered to normal patients). As with all thyroid preparations, thyroid gland function reflected by $T_{131}I$ thyroid uptake may be depressed by liothyronine. Useful $T_{131}I$ thyroid uptake values may be obtained, if necessary, usually within 2 weeks following withdrawal of the drug.

ADVERSE REACTIONS

Overdosage will produce signs and symptoms of hyperthyroidism, such as nervousness, cardiac arrhythmias, and angina pectoris.

DOSE AND ADMINISTRATION

Optimal dosage is usually determined by the patient's response. Confirmation tests include BMR, $T_{131}I$ Resin sponge uptake, $T_{131}I$ red cell uptake, Thyro Binding Index (TBI) and Achilles Tendon Reflex Test.

Mild hypothyroidism: recommended starting dose is 25 mcg. daily. Usual maintenance dose is 25-75 mcg. per day.

Myxedema: recommended starting dose is 5 mcg. daily. This may be increased by 5-10 mcg. daily every week or two until a maintenance dose of 50-100 mcg. per day is reached. After a daily dosage of 25 mcg., dosage may often be increased by 12.5-25 mcg. every 1-2 weeks.

Cretinism: Therapy must be started as soon as possible. Recommended starting dose is 5 mcg. daily with an increase of 5 mcg. every 3-4 days until desired response is obtained.

Simple (nontoxic) goiter: Initial dosage is 5 mcg. daily and may be increased by 5-10 mcg. per day every 1-2 weeks, with usual maintenance dose of 25-75 mcg. daily.

In the elderly or in children, therapy should be started with 5 mcg. daily and increased only by 5 mcg. increments at the recommended intervals.

OVERDOSAGE

(Use same information as described for thyroglobulin.)

D. *Claims permitted during extended period for obtaining substantial evidence.* Those claims for which sodium liothyronine is described in paragraph A3 above as possibly effective (not included in the labeling conditions in paragraph C) may continue to be used for 6 months following the date of this publication to allow additional time within which holders of previously approved applications or persons marketing the drug without approval may obtain and submit to the Food and Drug Administration, data to provide substantial evidence of effectiveness.

E. *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 Oct. 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.

b. Adequate data to assure the biologic availability of the drug in the formulation which is marketed. If such data are already included in the application, specific reference thereto may be made.

c. A supplement containing updating information as needed to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new

application form FD 356H to the extent described in the proposal for abbreviated new drug applications, § 130.4(f), published in the FEDERAL REGISTER February 27, 1969. (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--the supplement should be submitted under the provisions of section 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 biologic availability data.

c. 60 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding paragraphs 1 and 2 are acted upon. *Provided*, That within 60 days after the date of this publication the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement. (The labeling of sodium liothyronine may continue to include the claims referenced in paragraph D for the period stated.)

F. New applications. 1. Any other person who distributes or intends to distribute such drug which is intended for conditions of use for which it has been shown to be effective, as described under A above, should submit an abbreviated new drug application meeting the conditions specified in the proposed regulation, section 130.4(f) (1), (2), and (3), published in the FEDERAL REGISTER of February 27, 1969. Such applications should include proposed labeling which is in accord with the labeling conditions described herein and adequate data to assure the biologic availability of the drug in the formulation which is marketed or proposed for marketing.

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. (The labeling of sodium liothyronine may continue to include the claims referenced in paragraph D for the period stated.)

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

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

G. Exemption from periodic reporting. The periodic reporting requirements

of §§ 130.35(e) and 130.13(b)(4) are waived in regard to applications approved for these drugs solely for the conditions of use for which they are regarded as effective as described herein.

H. 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 recommended 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 a use other than the use provided for in this announcement, appropriate additional information as described in section 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 Marketed Drugs (MD-300), Bureau of Medicine 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 manufacturer, packer, or distributor of a drug of similar composition and labeling to the drug listed in this announcement or 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 reference number DESI 2245, and directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204:

Requests for NAS-NRC report: Press Relations Office (CE-300).

Supplements (identify with NDA number): Office of Marketed Drugs (MD-300), Bureau of Medicine.

Original abbreviated new drug applications: Office of Marketed Drugs (MD-300), Bureau of Medicine.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (MD-16), Bureau of Medicine.

This notice is issued pursuant to the 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 the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: September 18, 1969.

HERBERT L. LEY, JR.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-11398; Filed, Sept. 24, 1969; 8:45 a.m.]

ABBOTT LABORATORIES

Tranvet; Notice of Withdrawal of Approval of New-Drug Application

Amelco, Agricultural Division, Abbott Laboratories, North Chicago, Ill. 60064, holder of new-drug application No. 12-860V and all amendments and supplements thereto for the drug Tranvet (proprioprenazine hydrochloride), has waived opportunity for a hearing on the proposed withdrawal of approval of said application as announced in the FEDERAL REGISTER on February 19, 1969 (34 F.R. 2365).

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505 (e), 52 Stat. 1053, as amended; 21 U.S.C. 335(e)) and under authority delegated to him (21 CFR 2.120), finds that new evidence of clinical experience not contained in the application and not available to him until after the application was approved shows that the drug is not safe under the conditions of use on the basis of which the application was approved.

Therefore, pursuant to the foregoing finding, approval of new-drug application No. 12-860V and all amendments and supplements thereto applying to the drug Tranvet is withdrawn, effective on the date of signature of this document.

Dated: September 18, 1969.

J. K. Kirk,
Associate Commissioner
for Compliance.

[F.R. Doc. 69-11397; Filed, Sept. 24, 1969; 8:45 a.m.]

Office of the Secretary CHILD AND HEALTH WELFARE PROGRAM

Reorganization

Correction

In F.R. Doc. 69-11316 published in the issue of Tuesday, September 22, 1969, the date following "Sec. 7." in the third column on page 14762 should be changed to "September 17, 1969".

DEPARTMENT OF TRANSPORTATION

Coast Guard

[CGFR 69-96]

EQUIPMENT, CONSTRUCTION, AND MATERIALS

Approval Notice

1. Certain laws and regulations (46 CFR, Ch. I) require that various items of lifesaving, firefighting, and miscellaneous equipment, construction, and materials used on board vessels subject to Coast Guard inspection, on certain motorboats and other recreational vessels, and on the artificial islands and