CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-350

Generic Name:	Methimazole Tablets USP, 5mg and 10mg
Sponsor:	Par Pharmaceuticals
Approval Date:	March 29, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-350

CONTENTS

Reviews / Information Included in this ANDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

APPROVAL LETTER

ANDA 40-350

MAR 29 2000

Par Pharmaceuticals
Attention: Robert A. Femia, Ph.D.
U.S. Agent for: Genpharm Inc.
One Ram Ridge Road
Spring Valley, NY 10977

Dear Sir:

This is in reference to your abbreviated new drug application dated December 7, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Methimazole Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendments dated February 8, 1999; and February 2, March 8, March 10 and March 20, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methimazole Tablets USP, 5 mg and 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tapazole® Tablets, 5 mg and 10 mg, respectively, of Eli Lilly and Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the

proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ for JW 3/29/00

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

FINAL PRINTED LABELING

00578000

METHIMAZOLE TABLETS, USP

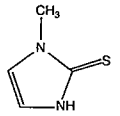
℞ only

DESCRIPTION

Methimazole (1-methylimidazole-2-thiol) is a white, crystalline substance that is freely soluble in water. It differs chemically from the drugs of the thiouracil series primarily because it has a 5- instead of a 6-membered ring.

Each tablet contains 5 or 10 mg (43.8 or 87.6 µmol) methimazole, an orally administered antithyroid drug. Each tablet also contains lactose, magnesium stearate, starch, and talc.

The molecular weight is 114.17, and the molecular formula is $C_4H_6N_2S$. The structural formula is as follows:



CLINICAL PHARMACOLOGY

Methimazole inhibits the synthesis of thyroid hormones and thus is effective in the treatment of hyperthyroidism. The drug does not inactivate existing thyroxine and triiodothyronine that are stored in the thyroid or circulating in the blood nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection.

The actions and use of methimazole are similar to those of propylthiouracil. On a weight basis, the drug is at least 10 times as potent as propylthiouracil, but methimazole may be less consistent in action.

Methimazole is readily absorbed from the gastrointestinal tract. It is metabolized rapidly and requires frequent administration. Methimazole is excreted in the urine.

In laboratory animals, various regimens that continuously suppress thyroid function and thereby increase TSH secretion result in thyroid tissue hypertrophy. Under such conditions, the appearance of thyroid and pituitary neoplasms has also been reported. Regimens that have been studied in this regard include antithyroid agents as well as dietary iodine deficiency, subtotal thyroidectomy, implantation of autonomous thyrotropic hormone secreting pituitary tumors, and administration of chemical goitrogens.

INDICATIONS AND USAGE

Methimazole is indicated in the medical treatment of hyperthyroidism. Longterm therapy may lead to remission of the disease. Methimazole may be used to ameliorate hyperthyroidism in preparation for subtotal thyroidectomy or radioactive iodine therapy. Methimazole is also used when thyroidectomy is contraindicated or not advisable.

CONTRAINDICATIONS

Methimazole is contraindicated in the presence of hypersensitivity to the drug and in nursing mothers because the drug is excreted in milk.

WARNINGS

Agranulocytosis is potentially a serious side effect. Patients should be instructed to report to their physicians any symptoms of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. The drug should be discontinued in the presence of agranulocytosis, aplastic anemia (pancytopenia), hepatitis, or exfoliative dermatitis. The patient's bone marrow function should be monitored.

Due to the similar hepatic toxicity profiles of methimazole and propylthiouracil, attention is drawn to the severe hepatic reactions which have occurred with both drugs. There have been rare reports of fulminant hepatitis, hepatic necrosis, encephalopathy, and death. Symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.) should prompt evaluation of liver function. Drug treatment should be discontinued promptly in the event of clinically significant evidence of liver abnormality including hepatic transaminase values exceeding 3 times the upper limit of normal.

Methimazole can cause fetal harm when administered to a pregnant woman. Methimazole readily crosses the placental membranes and can induce goiter and even cretinism in the developing fetus. In addition, rare instances of aplasia cutis, as manifested by scalp defects, have occurred in infants born to mothers who received methimazole during pregnancy. If methimazole is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus.

Since scalp defects have not been reported in offspring of patients treated with propylthiouracil, that agent may be preferable to methimazole in pregnant women requiring treatment with antithyroid drugs.

Postpartum patients receiving methimazole should not nurse their babies.

PRECAUTIONS

General

Patients who receive methimazole should be under close surveillance and should be cautioned to report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. In such cases, white-blood cell and differential counts should be made to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving additional drugs known to cause agranulocytosis.

Laboratory Tests

Because methimazole may cause hypoprothrombinemia and bleeding, prothrombin time should be monitored during therapy with the drug, especially before surgical procedures (see **General** under **PRECAUTIONS**).

Periodic monitoring of thyroid function is warranted, and the finding of an elevated TSH warrants a decrease in the dosage of methimazole.

00578000

Drug Interactions
The activity of anticoagulants may be potentiated by anti-vitamin-K activity attributed to methimazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2 year study, rats were given methimazole at doses of 0.5, 3, and 18 mg/kg/day. These doses were 0.3, 2 and 12 times the 15 mg/day maximum human maintenance dose (when calculated on the basis of surface area). Thyroid hyperplasia, adenoma, and carcinoma developed in rats at the two higher doses. The clinical significance of these findings is unclear.

Pregnancy Category D (See **WARNINGS**)
Methimazole used judiciously is an effective drug in hyperthyroidism complicated by pregnancy. In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently, a reduction in dosage may be possible. In some instances, use of methimazole can be discontinued 2 or 3 weeks before delivery.

Nursing Mothers
The drug appears in human breast milk and its use is contraindicated in nursing mothers (see **WARNINGS**).

Pediatric Use
(See **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Major adverse reactions (which occur with much less frequency than the minor adverse reactions) include inhibition of myelopoiesis (agranulocytosis, granulocytopenia, and thrombocytopenia), aplastic anemia, drug fever, a lupuslike syndrome, insulin autoimmune syndrome (which can result in hypoglycemic coma), hepatitis (jaundice may persist for several weeks after discontinuation of the drug), periarteritis, and hypoprothrombinemia. Nephritis occurs very rarely.

Minor adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesia, loss of taste, abnormal loss of hair, myalgia, headache, pruritus, drowsiness, neuritis, edema, vertigo, skin pigmentation, jaundice, sialadenopathy, and lymphadenopathy.

It should be noted that about 10% of patients with untreated hyperthyroidism have leukopenia (white-blood cell count of less than 4,000/mm^3), often with relative granulopenia.

OVERDOSAGE

Signs and Symptoms
Symptoms may include nausea, vomiting, epigastric distress, headache, fever, joint pain, pruritus, and edema. Aplastic anemia (pancytopenia) or agranulocytosis may be manifested in hours to days. Less frequent events are hepatitis, nephrotic syndrome, exfoliative dermatitis, neuropathies, and CNS stimulation or depression.

Although not well studied, methimazole-induced agranulocytosis is generally associated with doses of 40 mg or more in patients older than 40 years of age.

No information is available on the median lethal dose of the drug or the concentration of methimazole in biologic fluids associated with toxicity and/or death.

Treatment
To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the "Physicians' Desk Reference (PDR)". In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. The patient's bone marrow function should be monitored. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of methimazole.

DOSAGE AND ADMINISTRATION

Methimazole is administered orally. It is usually given in 3 equal doses at approximately 8-hour intervals.

Adults
The initial daily dosage is 15 mg for mild hyperthyroidism, 30 to 40 mg for moderately severe hyperthyroidism, and 60 mg for severe hyperthyroidism, divided into 3 doses at 8-hour intervals. The maintenance dosage is 5 to 15 mg daily.

Pediatric
Initially, the daily dosage is 0.4 mg/kg of body weight divided into 3 doses and given at 8-hour intervals. The maintenance dosage is approximately $^1/_2$ of the initial dose.

HOW SUPPLIED

Methimazole is available in:

The 5 mg tablets are white to off-white, round, flat-faced, bevelled-edged tablets, with "EM" 5 on one side and plain on the other.

They are available as follows:

- Bottles of 100	NDC 55567-080-18
- Bottles of 1000	NDC 55567-080-35
- Unit Dose packages of 100	NDC 55567-080-06

The 10 mg tablets are white to off-white, round, flat-faced, bevelled-edged tablets, with "EM" 10 on one side and plain on the other.

They are available as follows:

- Bottles of 100	NDC 55567-081-18
- Bottles of 1000	NDC 55567-081-35
- Unit Dose packages of 100	NDC 55567-081-06

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured by:
Genpharm Inc.
Toronto, Ontario
Canada M8Z 2S6
1-800-661-7134

005-780 REV. #00 March, 1999

NDC 55567-081-06

100 Tablets
Unit Dose

METHIMAZOLE

Tablets USP

10 mg

℞only

GENPHARM INC.

10 Blister Strips
of 10 Tablets

NDC 55567-081-06

100 Tablets
Unit Dose

METHIMAZOLE

Tablets USP

10 mg

℞only

GENPHARM INC.

10 Blister Strips
of 10 Tablets

NDC 55567-081-06

100 Tablets
Unit Dose

004-630 REV.#00

GENPHARM

Methimazole Tablets, USP
5 mg and 10 mg

Each tablet contains:
Methimazole 10 mg
USUAL DOSAGE: See package insert for dosage information.
Dispense in a tight, light-resistant container.
WARNING: This drug may cause toxic reactions. If such reactions occur, discontinue the drug. Constant supervision of patient is essential.
Keep tightly closed.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Printed in Canada
004-631 REV.#00

LOT:

EXP.:

NDC 55567-081-18 100 Tablets

METHIMAZOLE

Tablets USP

10 mg

Rx only

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

MAY 29

N 3 55567-081-18 5

Each tablet contains:
Methimazole 10 mg
USUAL DOSAGE: See package insert for dosage information.
Dispense in a tight, light-resistant container.
WARNING: This drug may cause toxic reactions. If such reactions occur, discontinue the drug. Constant supervision of patient is essential.
Keep tightly closed.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Package not child resistant
Printed in Canada
004-633 REV.#00

LOT:

EXP.:

NDC 55567-081-35 1000 Tablets

METHIMAZOLE

Tablets USP

10 mg

Rx only

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

MAY 29

N 3 55567-081-35 2

Response to MAJOR AMENDMENT dated May 13, 1999

NDC 55567-080-06

100 Tablets
Unit Dose

METHIMAZOLE

Tablets USP

5 mg

℞only

Manufactured by:
GENPHARM INC.
Toronto, Canada M8Z 2S6
1-800-661-7134

10 Blister Strips
of 10 Tablets

NDC 55567-080-06

METHIMAZOLE

Tablets USP

5 mg

100 Tablets
Unit Dose

Each tablet contains: Methimazole 5 mg.

USUAL DOSAGE: See accompanying package insert.

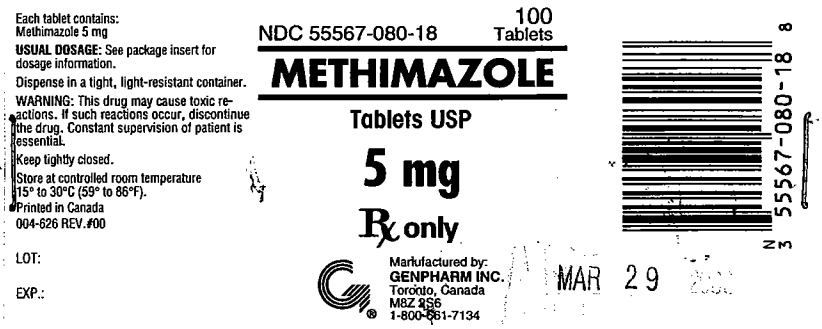
MAY 29

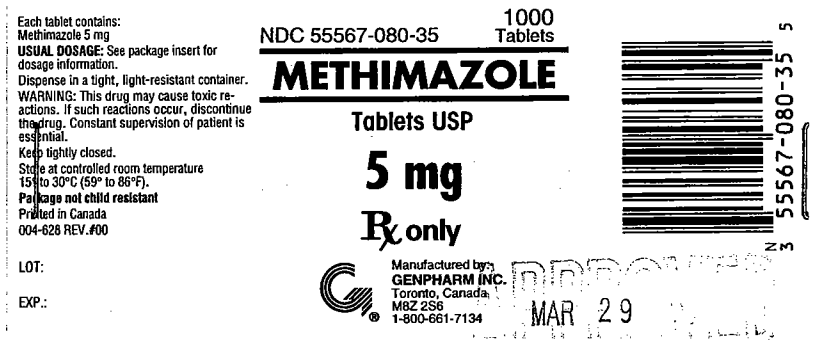
WARNING: This drug may cause toxic reactions. If such reactions occur discontinue the drug. Constant supervision of patient is essential.

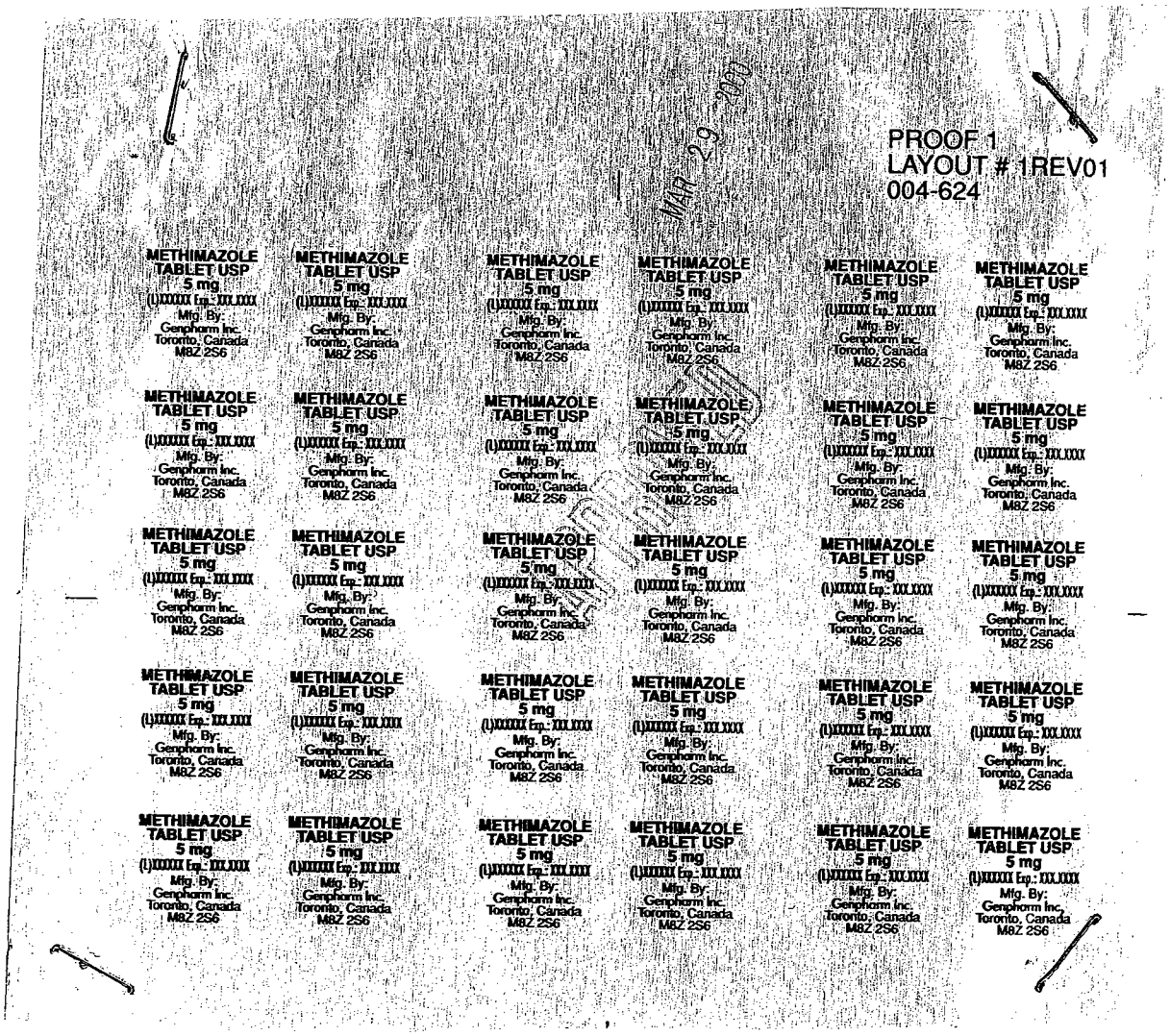
This package is not child resistant.

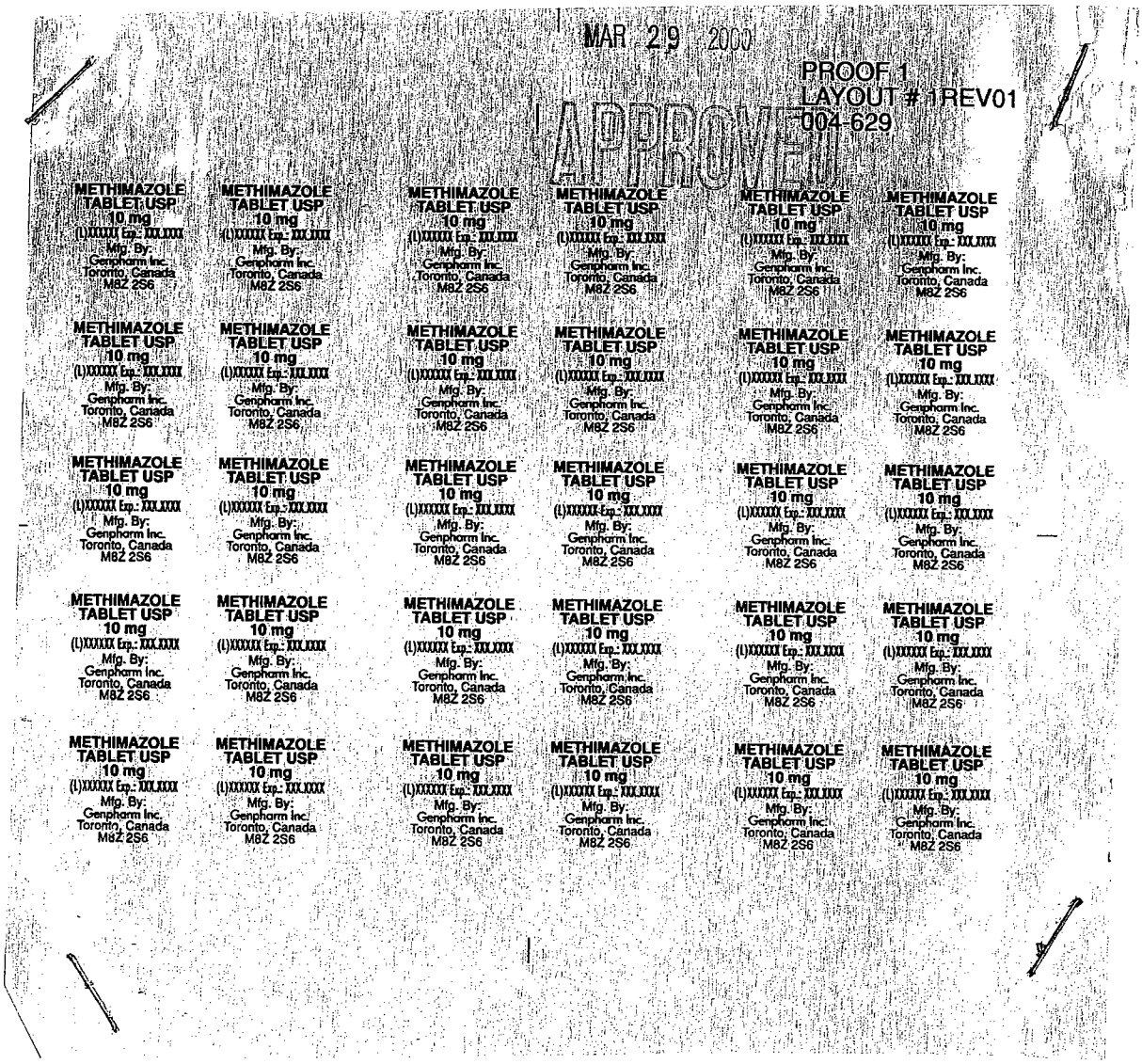
This is a bulk package and is not intended for dispensing.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).


Each tablet contains:
Methimazole 5 mg
USUAL DOSAGE: See package insert for dosage information.
Dispense in a tight, light-resistant container.
WARNING: This drug may cause toxic reactions. If such reactions occur, discontinue the drug. Constant supervision of patient is essential.
Keep tightly closed.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Printed in Canada
004-626 REV.#00
LOT:
EXP.:
NDC 55567-080-18
100 Tablets
METHIMAZOLE
Tablets USP
5 mg
℞ only
Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134
MAR 29
N 3 55567-080-18 8


Each tablet contains:
Methimazole 5 mg
USUAL DOSAGE: See package insert for dosage information.
Dispense in a tight, light-resistant container.
WARNING: This drug may cause toxic reactions. If such reactions occur, discontinue the drug. Constant supervision of patient is essential.
Keep tightly closed.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Package not child resistant
Printed in Canada
004-628 REV.#00
LOT:
EXP.:
NDC 55567-080-35
1000 Tablets
METHIMAZOLE
Tablets USP
5 mg
℞ only
Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134
MAR 29
N 3 55567-080-35 5


PROOF 1
LAYOUT # 1REV01
004-624
MAR 29 2000
METHIMAZOLE
TABLET USP
5 mg
(L)XXXXXX Exp.: XXX.XXXX
Mfg. By:
Genpharm Inc.
Toronto, Canada
M8Z 2S6


MAR 29 2000
PROOF 1
LAYOUT # 1REV01
004-629
APPROVED
METHIMAZOLE TABLET USP 10 mg
(L)XXXXXX Exp.: XXX.XXXX
Mfg. By:
Genpharm Inc.
Toronto, Canada
M8Z 2S6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-350 **Date of Submission: December 7, 1998**

Applicant's Name: Genpharm Inc.

Established Name: Methimazole Tablets USP, 5 mg and 10 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

2. CONTAINER (100's, 1000's, and 100 unit dose blister's)

   a. Satisfactory in draft.

3. CARTON (100 unit dose)

   a. Satisfactory in draft.

4. INSERT

   a. DESCRIPTION

      i. Revise the molecular weight to read "114.17" rather than '

   b. CLINICAL PHARMACOLOGY

      i. Revise to read "subtotal" in the last sentence of the last paragraph of this section.

   c. INDICATIONS AND USAGE

      i. Revise ' to read "Longterm" in the second sentence of this section.

   d. PRECAUTIONS

      i. Carcinogenesis, Mutagenesis, Impairment of Fertility

         Revise the second sentence to read as follows:

…12 times the 15 mg/day maximum…

e. ADVERSE REACTIONS

i. Revise the first sentence to read as follows:

…a lupuslike syndrome, insulin autoimmune syndrome…

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed containers labels for each strength and package size, along with 12 copies of final printed unit dose carton labeling and 12 copies of final printed insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: (100's, 1000's, and 100 unit dose blister's)

Unit Dose Blister Label:

Unit Dose Carton Label: (100's unit dose)

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: TAPAZOLE®

NDA Number: 07-517/S-018

NDA Drug Name: Methimazole Tablets USP

NDA Firm: Eli Lilly

Date of Approval of NDA Insert and supplement #: March 20, 1995
S-018

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labeling in jacket.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? For unit dose only.	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is TAPAZOLE®(Eli Lilly; NDA#07-517/S-018; Approved March 20, 1995).

2. The USP requires the product be preserved in well-closed, light-resistant containers.

3. The applicant certifies that any patents/exclusivities for this product have expired. See Vol. 1.1, page 23 and 25.

4. The product is manufactured by Genpharm Inc. 37 Advance Road, Etobicoke, Ontario, Canada, M8Z2S6. See Vol. 1.1, page 1317.

5. Other outside firms are utilized for testing purposes only. See Vol. 1.1, page 1343.

6. Container/Closure

100's(5mg & 10 mg)
Bottle: HDPE 60 mL
Child Resistant Cap: 33 mm
[redacted] &

1000's(5mg):
Bottle: 150 mL
Regular Cap: 38 mm
[redacted]

100's Unit dose
Blister (5 mg & 10 mg)
Foil Aluminum Push-Through
Film [redacted]

1000's(10mg):
Bottle: 200 mL
Regular Cap: 38 mm
[redacted]

See Vol. 1.7, page 1845.

7. Finished product

A white, crystalline substance that is freely soluble in water. See Vol. 1.1, page 47.

8. Product Line

5 mg-Bottles of 100 and 1000. Unit dose blisters of 100.
10mg-Bottles of 100 and 1000. Unit dose blisters of 100.

See Vol. 1.1, page 52.

9. Components/Composition

Innovator:
Active: Methimazole 5 mg or 10 mg
Inactive: starch
Lactose
Talc
Magnesium stearate

Applicant:
Active: Methimazole 5 mg or 10 mg
Inactive: starch
Lactose
Talc
Magnesium stearate

See Vol. 1.1, page 1216.

10. Storage/Dispensing:

NDA: Store at controlled room temperature, 59° to 86°F(15° to 30°C).

ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

See Vol. 1.1, page 52.

Date of Review: January 19, 1999
Date of Submission: December 7, 1998

Reviewer: /S/ **Date:** 2/17/99

Team Leader: **Date:**

/S/ 2/19/99

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-350 **Date of Submission:** July 9, 1999
Applicant's Name: Genpharm Inc.
Established Name: Methimazole Tablets USP, 5 mg and 10 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (100's and 1000's) Satisfactory as of July 9, 1999 submission.

Unit Dose Blister Label: (100's) Satisfactory as of July 9, 1999 submission.

Unit Dose Carton Label: (100's unit dose) Satisfactory as of July 9, 1999 submission.

Professional Package Insert Labeling: Satisfactory as of July 9, 1999.

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: TAPAZOLE®
NDA Number: 07-517/S-018
NDA Drug Name: Methimazole Tablets USP
NDA Firm: Eli Lilly

Date of Approval of NDA Insert and supplement #: March 20, 1995
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labeling in jacket.

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? For unit dose only.	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	

Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is TAPAZOLE®(Eli Lilly; NDA#07-517/S-018; Approved March 20, 1995).

2. The USP requires the product be preserved in well-closed, light-resistant containers.

3. The applicant certifies that any patents/exclusivities for this product have expired. See Vol. 1.1, page 23 and 25.

4. The product is manufactured by Genpharm Inc. 37 Advance Road, Etobicoke, Ontario, Canada, M8Z2S6. See Vol. 1.1, page 1317.

5. Other outside firms are utilized for testing purposes only. See Vol. 1.1, page 1343.

6. Container/Closure

100's(5mg & 10 mg)
Bottle: HDPE 60 mL
Child Resistant Cap: 33 mm

1000's(5mg):
Bottle: 150 mL
Regular Cap: 38 mm

100's Unit dose
Blister (5 mg & 10 mg)
Foil Aluminum Push-Through
Film

1000's(10mg):
Bottle: 200 mL
Regular Cap: 38 mm

See Vol. 1.7, page 1845.

7. Finished product

A white, crystalline substance that is freely soluble in water. See Vol. 1.1, page 47.

8. Product Line

5 mg-Bottles of 100 and 1000. Unit dose blisters of 100.
10mg-Bottles of 100 and 1000. Unit dose blisters of 100.

See Vol. 1.1, page 52.

9. Components/Composition

Innovator:
Active: Methimazole 5 mg or 10 mg
Inactive: starch
Lactose
Talc
Magnesium stearate

Applicant:
Active: Methimazole 5 mg or 10 mg
Inactive: starch
Lactose
Talc
Magnesium stearate

See Vol. 1.1, page 1216.

9. Storage/Dispensing:

NDA: Store at controlled room temperature, 59° to 86°F(15° to 30°C).

ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

See Vol. 1.1, page 52.

Date of Review: July 16, 1999
Date of Submission: July 9, 1999

Reviewer: /S/ **Date:** 7/16/99

Team Leader: /S/ **Date:** 7/16/1999

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cc:
ANDA: 40-350
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-350

FIRM: Genpharm

DOSAGE FORM: Tablets

STRENGTH: 5 mg, 10 mg

DRUG: Methimazole Tablets USP

cGMP STATEMENT/EIR UPDATED STATUS: *
EER pending ———

BIO STUDY:
The single-dose, fasting bioequivalence study for the 10 mg tablet has been found to be acceptable (review dated 3/5/99).

The waiver of in vivo bioequivalency study requirements for the 5 mg tablet was granted (review dated 3/5/99).

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not Applicable. The drug substance and drug product are compendial.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers (HDPE bottles and Blister) used in the stability studies are identical to those listed in container section.

Expiration dating period of 24 months for the drug product is acceptable.

LABELING:
Satisfactory per T. Watkins' review completed on 07-16-99.

STERILIZATION VALIDATION (IF APPLICABLE):
NOT APPLICABLE.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

Batch # AC30 (bio-batch)	Maximum batch size
——— tablets	——— tablets

* ——— is withdrawn per 3/20/00 amendment.
The EER is otherwise acceptable as of 8/6/99.
3/22/00

NDS Source:

Active DS	Methimazole, USP
DMF#	[redacted]
[redacted]	[redacted]
Last DMF update	03/24/99
DMF status	ADEQUATE The DMF was last reviewed by B. Cai on 02/22/00.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Batch # AC30 (10 mg)*	Batch # AC29 (5 mg)*
[redacted] tablets	[redacted] tablets
[redacted] of maximum batch size	[redacted] of maximum batch size

*MANUFACTURED VIA SAME PROCESS.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Strength	10 mg Tablets	5 mg Tablets
Compounding	[redacted]	[redacted]
Tableting	[redacted] tablets	[redacted] tablets

Bing Cai
Review Chemist
Division of Chemistry I
OGD/CDER
03/10/00

cc: ANDA 40-350
Division File
Field Copy

Endorsements:
HFD-625/BCai/03/10/9[illegible]
HFD-625/M.Smela/3/13/00
V:\firmsam\genpharm\ltrs&rev\40350.SUM.BBC.DOC
F/t by: gp/3/13/00

/s/ 3/17/00
/s/ 3/17/00

1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 40-350

3. **NAME AND ADDRESS OF APPLICANT**

Genpharm, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

4. **LEGAL BASIS FOR SUBMISSION**

Accepted by OGD. The referenced listed drug product is Tapazole®, 10 mg, manufactured by Eli Lilly & Company (NDA 7517).

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Methimazole

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

12/7/98 Original Submission
2/8/99 Bioequivalence Telephone Amendment

10. **PHARMACOLOGICAL CATEGORY**

Antihyperthyroid

11. **Rx or OTC**

R_x

12. **RELATED IND/NDA/DMF(s)**

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

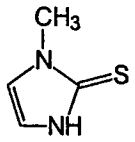
13. **DOSAGE FORM**

14. **POTENCY**

Tablet 5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE

2*H*-Imidazole-2-thione, 1,3-dihydro-1-methyl-
1-Methylimidazole-2-thiol



16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is not approvable. Inform the applicant of deficiencies.

19. REVIEWER: **DATE COMPLETED:**

Shirley S. Brown April 22, 1999

Redacted 20

Page(s) of trade secret and /or confidential commercial information

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2

2. **ANDA #** 40-350

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800) 661-7134

US Agent:
Mr. Robert A. Femia
Par pharmaceutical, Inc.
Telephone: (914) 425-7100

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Methimazole Tablets USP

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

12/07/98	Submission of ANDA
02/08/99	Telephone Amendment (Bioequivalency)
07/09/99	Major Amendment (CMC and Labeling)

FDA:

12/29/98	Acknowledgment (accept for filling: 12/11/99)
12/11/98	EERs were issued.
02/19/99	Label review (1st round), w/deficiencies.
03/05/99	Bio review-acceptable (Vol. 2.1).
05/13/99	CMC NA, Major (Vol. 2.1).
07/16/99	Labeling-acceptable (Vol. 3.1).

10. **PHARMACOLOGICAL CATEGORY**: Antihyperthyroid

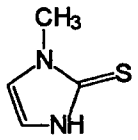
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
The RLD is Tapazole®, 10 mg from Eli Lilly & Company (NDA 07517). DMF: See DMF check list

13. **DOSAGE FORM**: Tablets

14. **POTENCY**: 5 mg, 10 mg

15. **CHEMICAL NAME AND STRUCTURE**:
2*H*-Imidazole-2-thione, 1,3-dihydro-1-methyl-
1-Methylimidazole-2-thiol
$C_4H_6N_2S$. 114.17.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EERs EERs acceptable as of 08/06/99, but needs revision.
- Labeling review: Acceptable (07/16/99)-Vol. 3.1.
- Bio-review: Acceptable (03/05/99)-Vol. 2.1.
- Micro: N/A
- MV: Not required (USP DS/DP)
- Minor CMC deficiencies could be found in item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (Minor Amendment).

19. **REVIEWER**: Bing Cai, Ph.D. **DATE COMPLETED**: 11/12/99 **DATE REVISED**: 01/04/00

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #** 40-350

3. **NAME AND ADDRESS OF APPLICANT:**

Genpharm Inc.
Attn: Mrs. Tirtho Uppal
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6
Telephone: (800) 661-7134

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Methimazole Tablets USP

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

12/07/98	Submission of ANDA
02/08/99	Telephone Amendment (Bioequivalency)
07/09/99	Major Amendment (CMC and Labeling)
02/02/00	Minor Amendment
03/09/00	Telephone Amendment
03/10/00	Telephone Amendment

FDA:

12/29/98	Acknowledgment (accept for filling: 12/11/99)
12/11/98	EERs were issued.
02/19/99	Label review (1st round), w/deficiencies.
03/05/99	Bio review-acceptable (Vol. 2.1).
05/13/99	CMC NA, Major (Vol. 2.1).
07/16/99	Labeling-acceptable (Vol. 3.1).
01/11/00	CMC NA, Minor (Vol. 3.1).
03/01/00	Telecons.

10. **PHARMACOLOGICAL CATEGORY**: Antihyperthyroid

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
The RLD is Tapazole®, 10 mg from Eli Lilly & Company (NDA 07517). DMF: See DMF check list

13. **DOSAGE FORM**: Tablets

14. **POTENCY**: 5 mg, 10 mg

15. **CHEMICAL NAME AND STRUCTURE**:
See CR#1

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EER: Pending
- DMF [redacted] Adequate;
- Labeling review: Acceptable (07/16/99)-Vol. 3.1.
- Bio-review: Acceptable (03/05/99)-Vol. 2.1.
- Micro: N/A
- MV: Not required (USP DS/DP)

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Approvable

19. **REVIEWER**: Bing Cai, Ph.D. **DATE COMPLETED**: 02/22/00 **DATE REVISED**: 03/10/00

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Addendum to Chemistry Review #3

ANDA Number: 40-350
Drug: Methimazole Tablets USP
Firm: Gempharm

Background:

This ANDA is approvable, except it is pending for an EER for its [redacted]

On 03/20/00, Genpharm provided a minor amendment to withdraw the above [redacted] **Genpharm will be responsible for complete analytical testing of the active drug substance including the test for [redacted] which was** [redacted] An analytical report for the [redacted] test for Methimazole [redacted] (lot 502994), which was performed by Genpharm, is provided. It is acceptable.

The ANDA is approvable.

Bing Cai
Review Chemist

Mike Smela
Team Leader

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APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA: 40-350 SPONSOR : Genpharm Inc.
DRUG & DOSAGE FORM : Methimazole Tablets, 10 mg & 5 mg

TYPE OF STUDY: SD (10 mg)
STUDY: XAcceptable

DISSOLUTION : XAcceptable

WAIVER: (5 mg)
XAcceptable

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: /S/ DATE : 2/23/99

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : /S/ DATE : 2/24/99

DIRECTOR: Dale P. Conner, Pharm.D. DIVISION OF BIOEQUIVALENCE
INITIAL : /S/ DATE : 3/5/99

APPEARS THIS WAY
ON ORIGINAL

2/

BIOEQUIVALENCY COMMENTS

ANDA: 40-350 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Methimazole Tablets, 10 mg & 5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

CC:ANDA 40-350
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang YH 2/24/99
HFD-617/ E. Hu [signature] 3/5/99
HFD-650/ D. Conner DR 3/5/99

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 12-11-98
02-08-99

1. FASTING STUDY (STF) Strengths: 10 mg
Clinical: [redacted]
Analytical: [redacted]
Outcome: AC

2. DISSOLUTION WAIVER (DIW) Strengths: 5 mg
Outcome: AC

3. Study Amendment (STA) Strengths: 10 mg
Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

Methimazole Tablets USP
ANDA #40-350: 5 mg & 10 mg
Reviewer: Hoainhon Nguyen
W #40350sdw.d98

Genpharm Inc.
Ontario, Canada
Submission Date:
December 11, 1998
February 8, 1999*
(*Telephone Amendment)

Review of a Bioequivalence Study, Dissolution Data and a Waiver Request

I. Background:

Methimazole is a thioamide antithyroid agents, indicated in the treatment of hyperthyroidism and as an adjunct to ameliorate hyperthyroidism in preparation for surgical treatment or radioactive iodine therapy. Methimazole inhibits the synthesis of thyroid hormones by interfering with the incorporation of iodine into tyrosyl residues of thyroglobulin; the drug also inhibits the coupling of these iodotyrosyl residues to form iodothyronine. The drug does not inactivate existing thyroxine and triiodothyronine that are stored in the thyroid or circulating in the blood nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection. Methimazole is freely soluble in water.

Methimazole is rapidly absorbed from the GI tract following oral administration with peak plasma concentrations occurring within about 1 hour. Methimazole readily crosses the placenta and is distributed into milk in concentrations approximately equal to those in maternal serum. The elimination half-life of methimazole reportedly ranges from about 5-13 hours. The drug is excreted in urine. In one study, about 12% of a dose was excreted in urine within 24 hours.

Adverse reactions to methimazole reportedly occur in less than 3% of patients receiving the drug. Adverse dermatologic effects are most commonly reported. Minor adverse effects of the drug include rash, urticaria, pruritus, abnormal hair loss, skin pigmentation, edema, nausea, vomiting, epigastric distress, loss of taste, arthralgia, myalgia, paresthesia, and headache. Drowsiness, neuritis, vertigo, sialadenopathy, and lymphadenopathy have also

occurred in patients receiving the drug.

The usual initial adult dosage of methimazole is 15, 30-40, or 60 mg daily for the treatment of mild, moderately severe, or severe hyperthyroidism, respectively. The adult maintenance dosage generally ranges from 5-30 mg daily, given in 3 equally divided doses at approximately 8-hour intervals.

The RLD product of methimazole is Tapazole (scored) Oral Tablets, 5 and 10 mg, manufactured by Eli Lilly.

The firm has submitted the results of a fasting, single-dose bioequivalence study comparing its Methimazole Tablets USP, 10 mg, with Eli Lilly's Tapazole® 10 mg Tablets. Comparative dissolution data for the test and RLD products of all strengths are also submitted in support of the *in vivo* bioequivalence study waiver requests for the 5 mg strength of the test product.

Telephone amendment dated February 8, 1999 contains the long-term stability data requested.

II. Bioequivalence Study:

FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #970732): "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Genpharm and Jones (Tapazole®) 10 mg Methimazole Tablets in Healthy Adult Males under Fasting Conditions"

Study Objective: Bioequivalency of Genpharm and Jones' (Tapazole®) 10 mg Methimazole Tablets under fasting conditions.

Study Facilities/Dates/Investigators:

Clinical: [redacted] April 20 and May 4, 1998; [redacted]

Analytical: [redacted] between July 6 and 13, 1998; [redacted]

Study Design: 2-treatment, 2-period, randomized crossover

Demographics: 26 normal, healthy male volunteers; 18-40 years of age; mean height 175 cm; mean weight 73 kgs participated in the study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Pages 124-5, Vol. 1.1

Restrictions:

No prescription and OTC medications for at least 7 days prior to the study and no concomitant medications during the study sessions.

No alcoholic beverages and no , grapefruit- or xanthine-containing beverages or food for 24 hours prior to and during the study period.

No food for overnight prior to and for 4 hours postdose.

Washout: 14 days.

Confinement: From the evening pre-dose to approximately 36 hours post-dose.

Treatments and Sampling:

Treatment A(Test Product): One of Genpharm's Methimazole 10 mg tablets, lot # AC302 (Batch size of ——— units, potency of 100.2%); proposed exp. date: 3/2000.

Treatment B(Reference Product): One of Jones' Tapazole® 10 mg methimazole tablets, lot # 1ND95M (Potency: 101.3%); exp. 1/2000.

Blood samples collected: predose, 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.66, 0.833, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 hours postdose. Plasma samples were stored at -12°C pending assay.

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Results:

All twenty-six enrolled volunteers completed the clinical portion of the study. First 24 subjects were analyzed per protocol.
There was no significant difference (alpha=0.05) between treatments for LAUC(0-T), LAUC(0-Inf) or LCMAX. The results are summarized in the tables below:

Table I
Methimazole Comparative Pharmacokinetic Parameters
Dose=10 mg; n=24
Fasting Study

Parameters	Test Mean(CV%)	Reference Mean(CV%)	90% C.I.	Ratio T/R
AUC(0-T) ng.hr/mL	1503*	1532*	[0.92;1.04]	0.98
AUC(0-Inf) ng.hr/mL	1549*	1575*	[0.92;1.05]	0.98
CMAX ng/mL	256.9*	251.3*	[0.91;1.15]	1.02
TMAX (hrs)	0.658(68)	0.624(71)		
KEL (1/hrs)	0.128(17)	0.127(17)		
T1/2 (hrs)	5.58(18)	5.64(18)		

*Geometric LSMeans

APPEARS THIS WAY
ON ORIGINAL

Table II
Comparative Mean Plasma Levels of Methimazole
Dose=10 mg; n=24
ng/ml(CV%)
Fasting Study

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B
0	0.00 (0)	0.00 (0)
0.083	2.013 (145)	0.474 (350)
0.17	28.67 (135)	15.71 (113)
0.25	102.4 (91)	95.61 (75)
0.33	170.1 (69)	166.1 (55)
0.42	209.4 (49)	212.0 (32)
0.50	223.1 (42)	237.3 (34)
0.66	217.3 (24)	209.8 (26)
0.83	189.5 (20)	202.4 (20)
1.00	184.6 (15)	190.3 (14)
1.50	168.8 (13)	166.9 (10)
2	155.2 (13)	156.4 (12)
2.50	146.7 (16)	148.5 (12)
3	137.9 (16)	139.4 (13)
4	122.7 (16)	122.9 (14)
6	92.92 (19)	95.25 (20)
8	72.16 (24)	71.09 (23)
12	38.46 (32)	39.61 (31)
24	9.453 (46)	10.06 (51)
36	1.893 (130)	2.052 (117)
AUCT [ng.hr/mL]	1534 (20)	1562 (20)
AUCI [ng.hr/mL]	1580 (20)	1605 (20)
Cmax [ng/mL]	268.1 (31)	261.3 (29)

Intra-subject CV%'s per ANOVA tables are as follows: for lnAUCT, 12.4; lnAUCI, 12.4; and lnCMAX, 24.2.

Adverse Effects:

There was no study drug related adverse reactions reported.

III. Dissolution Testing: USP's method

Drug (Generic Name): Methimazole Tablets USP Firm: Genpharm
Dose Strength: 5 mg & 10 mg ANDA# 40-350
Submission Date: December 11, 1998

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket X Paddle __ RPM 100 rpm Units Tested: 12
Medium: Water Volume: 500 ml
Reference Drug: (Manuf.) Tapazole Tablets (Lilly)
Assay Methodology: [illegible]
Specifications: NLT 80% in 30 minutes

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # AC29 Strength (mg) 5		Reference Product Lot # OMR66N Strength (mg) 5	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
5	98.1 (10)	[illegible]	50.5(32)	[illegible]
10	102 (4.4)	[illegible]	95.7(17)	[illegible]
20	102(4.3)	[illegible]	98.7(6.7)	[illegible]
30	102(4.3)	[illegible]	99.9(3.0)	[illegible]

Sampling Times (Min.)	Test Product Lot # AC30 Strength (mg) 10		Reference Product Lot # 1ND95M Strength (mg) 10	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
5	98.1 (3.4)	[illegible]	70.1(20)	[illegible]
10	101 (3.1)	[illegible]	97.5(5.8)	[illegible]
20	101(3.2)	[illegible]	101(1.3)	[illegible]
30	101(3.2)	[illegible]	101(1.2)	[illegible]

NOTE: F2 Similarity factor for dissolution data between strengths of the test product

was not calculated due to the fast release rate (i.e., greater than 80% dissolved in 5 minutes).

IV. Comments:

1. The single-dose, fasting bioequivalence for the 10 mg strength demonstrates that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) under fasting conditions.

2. The in vitro dissolution data for the test and reference products of all strengths are acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP XXIII apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. The formulations of the 5 mg strength of the test product are proportionally similar to that of the 10 mg strength, which underwent the bio study (See comparative formulations attached).

4. NOT FOR RELEASE UNDER FOI: The formulations of the RLD product, 10 mg and 5 mg, are included in this review for reference (per COMIS):

Ingredient	5 mg Formulation	10 mg Formulation
Methimazole	5 mg	10 mg
Lactose	[redacted]	[redacted]
Starch	[redacted]	[redacted]
Talc	[redacted]	[redacted]
Magnesium Stearate	[redacted]	[redacted]

V. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Genpharm on the test product, Methimazole Tablets, 10 mg, lot # AC30, comparing it with the reference product, Lilly's Tapazole® 10 mg Tablets, lot # 1ND95M, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Genpharm's Tapazole Tablets, 10 mg, is bioequivalent to the reference product, Lilly's Tapazole® 10 mg Tablets, under fasting conditions.

2. The in-vitro dissolution testing conducted by Genpharm on its Methimazole Tablets, 10 mg and 5 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP XXIII apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. The firm has demonstrated that the formulation of its Methimazole Tablets, 5 mg, is proportionally similar to that of the 10 mg strength that underwent acceptable in vivo bioequivalence testing. The requests for waiver of in vivo bioequivalence study requirements for the 5 mg tablets is granted. The firm's Methimazole Tablets, 5 mg, is therefore deemed bioequivalent to Lilly's Tapazole®Tablets, 5 mg.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/ 2/24/99

Concur: /S/ Date: 3/5/99

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

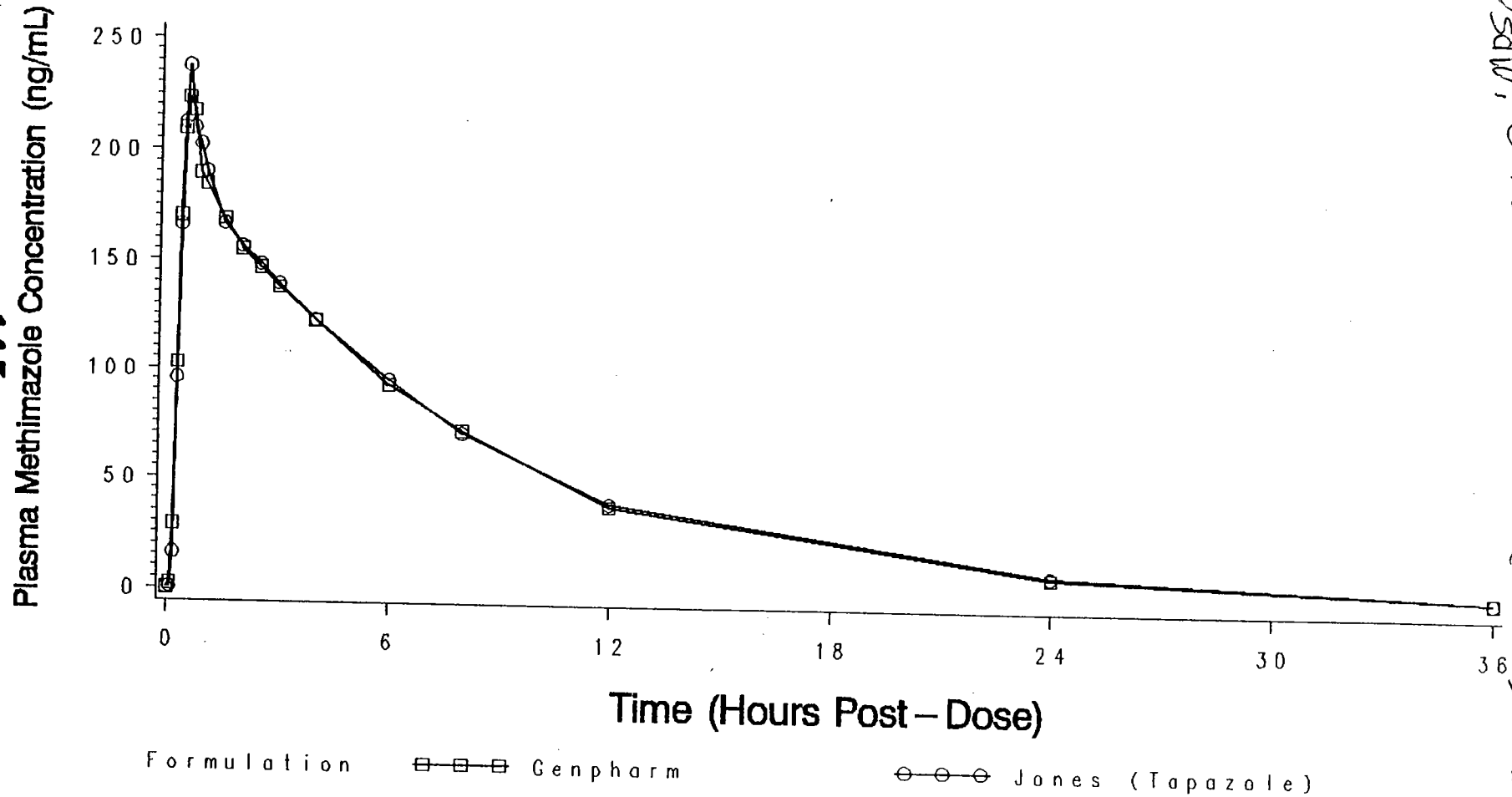
cc: ANDA # 40-350 (original, duplicate), HFD-652(Huang, Nguyen),
Drug File, Division File
HNguyen/01-28-99/W #40350sdw.d98
Also as V:\firmsam\genpharm\ltrs&rev\40350sdw.d98
Attachment: 2 pages

Figure 2

Project No. 970732

Mean Plasma Methimazole Concentrations

(Linear Plot)



115

W# 40370sdw, d 98 Attachment (1 of 2) 18

DEFAULT (16JUL98)

GENPHARM

W# 40350sdw. d 98 Attachment (2 of 2

PROPORTIONALITY DATA

Methimazole Tablets, USP
5 mg and 10 mg

Dosage Strength			5 mg		10 mg	
No.	Ingredient	Std	Amount per Tablet (mg)	Amount per Tablet (%)	Amount per Tablet (mg)	Amount per Tablet (%)
1.	Methimazole	USP	5.0	[redacted]	10.0	6.67
2.	Starch [redacted]	NF	[redacted]			
3.	Lactose Monohydrate [redacted]	NF	[redacted]			
4.	Talc	USP	[redacted]			
5.	Magnesium Stearate	USP	[redacted]			
Tablet Weight			75.0	100.0%	150.0	100.0%

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Bing Cai, Review Chemist; Michael J. Smela, Jr., Team Leader
DATE: 03/01/00

NAME/TITLE OF INDIVIDUAL(S): MS Tirtho Uppal
FIRM: Genpharm
PRODUCT NAME: Methimazole Tablets USP
TEL #: 800-661-7134
Reference: ANDA 40-350

Notes of Conversation:

Mike Smela advised that there were some minor issues need to be resolved before the reference ANDA can be approved.

Bing Cai then provided more detail regarding our concerns:

1. The proposed Limit for _____ (NMT _____ is too lax and needs to be tightened.

2. The proposed limit for Particle Size (control only _____ of particles) needs to be revised and tightened.

3. For _____ Assay, we recommended that the firm might increase the sample size for the 5 mg tablets so that the total amount of the sample is the same as that of the 10 mg. However, the BUA should **remain as "mean of _____ with RSD NMT _____**

3. The stability data for batch AC291 (5 mg, bottles of 100) shows a significant potency drop _____ from 0 month to 20 month. Need comments or additional supporting data for this stability study.

MS Uppal acknowledged above comments. During the conversation, she also raised following questions/comments:

1. The amount of _____ in the DS may effect the _____ test. Mike said that they could provide explanation/supporting data.

2. For Particle Size Controls, is _____ level of control acceptable? Mike said yes.

In addition, Mike Smela explained our telephone amendment policy and MS Uppal said that she understood. She committed to provide a telephone amendment as soon as possible.

SIGNATURE OF OGD REPRESENTATIVES:

/S/

Bing Ca-

/S/

Mike Smela

Location of Electronic Copy:

V:\FIRMSAM\GENPHARM\TELECONS\40350.DOC

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ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

archival

1.1

Application: ANDA 40350/000
Stamp: 11-DEC-1998
Regulatory Due:
Applicant: GENPHARM
1 RAM RIDGE RD
SPRING VALLEY, NY 10977
Priority:
Org Code: 600

Action Goal:
District Goal: 11-NOV-1999
Brand Name:
Estab. Name: METHIMAZOLE
Generic Name:

Dosage Form: (TABLET)
Strength: 5MG & 10MG

Application Comment:
FDA Contacts: D. HUIE (HFD-615) 301-827-5862 , Project Manager
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:
Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-JAN-1999				DAVISG

Establishment:
GENPHARM INC
214 NORSEMAN
ETOBICOKE, ONTARIO, CA

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: THIS SITE DOES THE STABILITY TESTING OF THE FINISHED PRODUCT. THERE IS ALSO A SITE AT 212 NORSEMAN STREET THAT DOES THE BOTTLING(PACKAGING) OF THE FINISHED PRODUCT (on 13-JAN-1999 by G. DAVIS (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-JAN-1999				DAVISG

Establishment: 9690013
GENPHARM INC PHARMACEUTICALS
37 ADVANCE RD, M8Z 2S6
ETOBICOKE, ONTARIO, CA

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCM OAI Status: NONE
Estab. Comment: THIS SITE DOES THE MANUFACTURING, SOME OF THE PACKAGING AND LABELING AND SOME OF THE TESTING OF THE FINISHED PRODUCT (on 07-JAN-1999 by G. DAVIS (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-JAN-1999				DAVISG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350

CORRESPONDENCE

GENPHARM

ORIG AMENDMENT
NJAM

TELEPHONE AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Telephone Amendment to ANDA #40-350
Methimazole Tablets USP
5 mg and 10 mg

This **Telephone Amendment** to our abbreviated new drug application is being sent in response to a telephone request of March 10, 2000 from Dr. Bing Cai, Chemistry Reviewer.

For the reviewers' convenience, we have presented our response in a comment/response format. The telephone comments have been presented in **bold** followed by our response and supporting documents where applicable.

This amendment consists of one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at (416)207-1216 or you may contact our U.S. agent, Mr. Robert A. Femia of Par Pharmaceutical, Inc. at (914)425-7100.

Yours sincerely,

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

MAR 10 2000
Date

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 16 2000
OGD

85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

COVER SHEET

GENPHARM

FAX

To: Dr. Bing Cai, Chemistry Reviewer
Fax #: 301-594-0180
Subject: Methimazole Tablets 5 & 10 mg, ANDA 40-350 - **Telephone Amendment**
Date: March 10, 2000
Pages: 6 , including this cover sheet.

Dear Dr. Cai:

Further to the telephone conversation of today March 10, 2000 with Dr. Peter Persicaner, Mr. Craig Judy and myself with regard to ANDA 40-350 for Methimazole Tablets USP, 5 mg & 10 mg, please find presented our **Telephone Amendment** in response to the comment made in the telephone conversation with regard to the limits for particle size testing.

As per your instruction, we are faxing the Telephone Amendment containing the drug substance specification that has been revised to clarify the upper and lower limits for particle size.

We will follow up with a hard copy that will contain the signed cover letter from Genpharm and a signed version of the FDA 356h form from our US Agent. The hard copy will be provided as one Archive, one Review and one Field Copy.

If you have any questions or concerns please contact the undersigned or Ms. Tirtho Uppal at 416-207-1216.

Sincerely,

Donna Hillier
Senior Associate, Regulatory Affairs

From the desk of...

Donna Hillier
Regulatory Affairs Senior Associate
Genpharm Inc.
85 Advance Road
Etobicoke, ON M8Z 2S9

416-236-2631, Ext 245, Direct 207-1210
Fax: 416-236-4363

Comment 1: Please provide clarification as to the limits for particle size as it appears from the scans for the batches provided in Telephone Amendment dated March 9, 2000 that all batches are failing the lower limit.

Response 1: Presented is the specification TS003937.4 for Methimazole, USP that contains a revision to clarify the limits previously established for particle size in the Telephone Amendment dated March 9, 2000.

The particle size limit has been revised to NLT [redacted] ; NLT [redacted] based on data from the lot used in the bio-study batch of drug product and a telephone conversation between Dr. Bing Cai, Chemistry Reviewer, FDA and Dr. Peter Persicaner, VP Formulation Development, Mr. Craig Judy, Manager, Formulation Development and Ms Donna Hillier, Senior Associate, Regulatory Affairs, Genpharm Inc., in which the proposed limits and interpretation of the scans previously presented were discussed.

APPEARS THIS WAY
ON ORIGINAL

Pgs 1 of 3
Specs & analysis

Redacted 4

pages of

trade secret and/or

confidential

commercial

information

COVER SHEET

GENPHARM

FAX

To: Dr. Bing Cai, Chemistry Reviewer
Mr. Mike Smela, Project Manager, FDA, OGD

Fax #: 301-594-0180

Subject: Methimazole Tablets 5 & 10 mg, ANDA 40-350

Date: March 9, 2000

Pages: 22 , including this cover sheet.

Dear Dr. Cai and Mr. Smela:

Further to your telephone conversation with Ms. Tirtho Uppal of Genpharm with regard to ANDA 40-350 for Methimazole Tablets USP, 5 mg & 10 mg, please find presented our Telephone Amendment in response to the comments made in the telephone conversation.

We have addressed the issues of [redacted], Particle Size, [redacted], and Stability as per the discussion.

As per your instruction, we are faxing the response within the 10 day timeframe and will follow up with a hard copy response that will contain the signed version of the FDA 356h form from our US Agent. The hard copy will be provided as one Archive, one Review and one Field Copy.

If you have any questions or concerns please contact the undersigned or Ms. Tirtho Uppal at 416-207-1216.

Sincerely,

Donna Hillier
Senior Associate, Regulatory Affairs

From the desk of...

Donna Hillier
Regulatory Affairs Senior Associate
Genpharm Inc.
85 Advance Road
Etobicoke, ON M8Z 2S9

416-236-2631, Ext 245, Direct 207-1210
Fax: 416-236-4363

GENPHARM

TELEPHONE AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Telephone Amendment to ANDA #40-350
Methimazole Tablets USP
5 mg and 10 mg

This **Telephone Amendment** to our abbreviated new drug application is being sent in response to a telephone request of March 2, 2000 from Dr. Bing Cai, Chemistry Reviewer and Mr. Mike Smela, Team Leader to the undersigned.

For the reviewers' convenience, we have presented our response in a comment/response format. The telephone comments have been presented in **bold** followed by our response and supporting documents where applicable.

This amendment consists of one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at (416)207-1216 or you may contact our U.S. agent, Mr. Robert A. Femia of Par Pharmaceutical, Inc. at (914)425-7100.

Yours sincerely,

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

March 8/2000
Date

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

Table of Contents

APPEARS THIS WAY
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genpharm Inc.	
TELEPHONE NO. *(Include Area Code)* 1-416-207-1216	FACSIMILE (FAX) Number *(Include Area Code)* 1-416-236-4363
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 37 Advance Road, Etobicoke, Ontario, Canada, M8Z 2S6	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: Robert A . Femia, Ph.D, Vice-President, Scientific & Regulatory Affairs, Par Pharmaceuticals, One Ram Ridge Road, Spring Valley, NY 10977, Tel: (914)425-7100, ext 208, Fax: (914)425-7907

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 40-350

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Methimazole, USP	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
1-Methylimidazole-2-thiol	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	5 mg and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Indicated in the medical treatment of hyperthyroidism.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
- ☐ NEW DRUG APPLICATION (21 CFR 314.50)
- ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
- ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Tapazole — Holder of Approved Application Eli Lilly & Company

TYPE OF SUBMISSION (check one)
- ☐ ORIGINAL APPLICATION
- ☒ AMENDMENT TO A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ SUPAC SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

REASON FOR SUBMISSION Response to a Telephone Amendment of March 2, 2000.

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to Original ANDA # 40-350

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

Please refer to Original ANDA # 40-350

This application contains the following items: *(Check all that apply)*	
X	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to a Telephone Amendment of March 2, 2000.

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Robert A. Femia Ph.D Vice-President, Scientific & Regulatory Affairs	DATE
ADDRESS *(Street, City, State, and ZIP Code)* Par Pharmaceuticals, One Ram Ridge Road, Spring Valley, NY 10977		Telephone Number (914)425-7100, Ext 208

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

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commercial

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GENPHARM

N/A 41

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: Minor Amendment to ANDA #40-350
Methimazole Tablets USP
5 mg and 10 mg

This **Minor Amendment** to our abbreviated new drug application is being sent in response to your letter dated January 11, 2000 containing chemistry and manufacturing deficiencies.

For the reviewers' convenience, we have presented our response in a comment/response format. The reviewers comments have been presented in **bold** followed by our response and supporting documents where applicable.

We have enclosed one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.96. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at (416)207-1216 or you may contact our U.S. agent, Mr. Robert A. Femia of Par Pharmaceutical, Inc. at (914)425-7100.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 04 2000
OGD

Yours sincerely,

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

Feb 2nd 2000
Date

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

FPL
ORIG AMENDMENT
AC

Re: Major Amendment to ANDA #40-350
Methimazole Tablets USP
5 mg and 10 mg

This **Major Amendment** to our abbreviated new drug application is being sent in response to your letter dated May 13, 1999.

For the reviewers' convenience, we have presented our response in a comment/response format. The reviewers comments have been presented in **bold** followed by our response and supporting documents where applicable.

We have enclosed one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs. The labeling comments have been addressed and final printed labels are provided as volume 2 of 2 of the archival and review copies.

At this time we are submitting an amendment to our application to include [redacted] as a site of [redacted] Supporting documentation for Section X[redacted] has been presented in Volume 1 of 2 immediately following the Major Amendment response.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Robert A. Femia of Par Pharmaceutical, Inc. at (914)-425-7100.

Yours sincerely,

Mrs. Tirtho Uppal
Director, Regulatory Affairs

JUL 09 1999
Date

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GENPHARM

May 13, 1999

NEW CORR
NC
NAI
DA 5/21/99

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ACKNOWLEDGEMENT

Re: Methimazole Tablets 5 mg and 10 mg (ANDA # 40-350)

We acknowledge receipt of the ***MAJOR AMENDMENT*** letter, dated May 13, 1999 from Ms. Denise Huie, project manager of the Office of Generic Drugs, CDER, FDA.

We would like to inform you that we are currently addressing the comments made by the reviewer and will file an amendment when the response is complete.

If there are any further questions or comments with respect to this application, you may direct written and telephoned communications to Genpharm at 1-416-207-1216 or you may contact our U.S. agent, Mr. Robert A. Femia, of Par Pharmaceutical Inc. at (914) 425-7100.

Yours sincerely

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

May 13, 1999
(date)

cc: Mr. Robert A. Femia
Vice President Scientific & Regulatory Affairs
Par Pharmaceutical Inc.
One Ram Ridge Road
Spring Valley, NY 10977

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 19 1999
OGD

5.20.99

GENPHARM

AB

February 8, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE TELEPHONE AMENDMENT

Re: ANDA #: 40-350
Methimazole Tablets USP
5 mg & 10 mg

Please find enclosed a ***BIOEQUIVALENCE TELEPHONE AMENDMENT*** to ANDA # 40-350 in response to Dr. Nasser Mahmud's telephone request on January 29, 1999 pertaining to long term stability for the biostudy for the above referenced product.

We have enclosed one (1) archival and one (1) pharmacokinetic review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-800-661-7134 or you may contact our US agent, Mr. Robert A. Femia at (914) 425-7100.

Yours sincerely

Feb 8/99
(date)

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

cc: Mr. Robert A. Femia
Vice President, Scientific and Regulatory Affairs
Par Pharmaceuticals, Inc.
One Ram Ridge Road
Spring Valley, New York
USA, 10977

RECEIVED
FEB 1 1 1999
GENERIC DRUGS

ANDA 40-350

Par Pharmaceuticals Inc.
U.S. Agent for: Genpharm Inc.
Attention: Robert A. Femia, Ph.D.
One Ram Ridge Road
Spring Valley, NY 10977

DEC 29 1998

Dear Sir:

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

NAME OF DRUG: Methimazole Tablets USP, 5 mg and 10 mg

DATE OF APPLICATION: December 7, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 11, 1998

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 ANDA number shown above.

Should you have questions concerning this application, contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GENPHARM

505(j)(2)(A) OK
12/23/98
S

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA

Re: Abbreviated New Drug Application
Methimazole Tablets USP
5 mg and 10 mg

We are pleased at this time to submit an original Abbreviated New Drug Application for our product - Methimazole Tablets USP 5 mg and 10 mg.

The purpose of this application is to gain FDA approval to market Methimazole Tablets 5 mg and 10 mg, in the U.S.A. The drug product described above is the same as the Brand Product Tapazole® Tablets 5 mg and 10 mg, manufactured by Brand Manufacturer Eli Lilly and Company. We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form, comparing active ingredient, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Genpharm Inc. and by Brand Manufacturer Eli Lilly and Company.

We have enclosed one (1) archival, one (1) chemistry review, one (1) pharmacokinetic review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA. The number of volumes in the archival, review and field copies of the ANDA are as follows:

Blue Archival Copy	8 volumes
Orange Review Copy	4 volumes
Red Review Copy	4 volumes
Burgundy Field Copy	4 volumes.

We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

This application contains a Bioequivalence electronic submission ESD.

RECEIVED
DEC 11 1998
GENERIC

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In addition, for the Bioequivalence Section, we have enclosed in duplicate, two computer diskettes containing a Bioequivalence electronic submission ESD (BA/BE EVA) in the format prescribed by the FDA. The duplicate diskettes are located at the front cover of the ARCHIVAL Copy of this application. We certify that, to the best of our knowledge, the data entered into the BA/BE EVA ESD are identical to or can be derived from the information contained in the hard copy submission.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-800-661-7134 or you may contact Mr. Robert A. Femia at (914) 425-7100.

A letter of authorization, allowing Mr. Robert A. Femia, Par Pharmaceutical Inc. to act as our U.S. agent, is included in Section XX.of this application.

Yours sincerely

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

DEC 07 1998
(date)

cc: Mr. Robert A. Femia
Vice President, Scientific and Regulatory Affairs
Par Pharmaceuticals, Inc.
One Ram Ridge Road
Spring Valley, New York
USA, 10977