CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

Generic Name: Methimazole Tablets USP 20mg

Sponsor: King & Spalding

Approval Date: June 7, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

CONTENTS

Reviews / Information Included in this ANDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

APPROVAL LETTER

ANDA 40-350/S-001, S-002, S-003 and S-004

JUN 7 2001

King & Spalding
U.S. Agent for: Genpharm Inc.
Attention: Eugene Pfeifer
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-4706

Dear Sir:

This is in reference to your supplemental new drug applications dated October 19, 2000, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Methimazole Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendment dated May 4, 2001.

The supplemental applications, submitted as "Prior Approval Supplements", provide for the following changes:

S-001 A new 20 mg strength,

S-002 Associated control revisions,

S-003 Associated packaging,

S-004 Associated labeling.

We have completed the review of these supplemental applications and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the supplemental applications are approved. When used as recommended in the labeling, the drug product, Methimazole Tablets 20 mg, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness.

We remind you that you must comply with the requirement for an approved abbreviated application described 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,

Gary Buehler 6/7/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

FINAL PRINTED LABELING

METHIMAZOLE TABLETS, USP

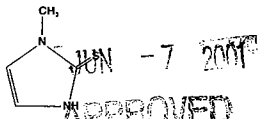
℞ only

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, 10, or 20 mg (43.8, 87.6 or 175.2 μmol) methimazole, an orally administered antithyroid drug. Each tablet also contains lactose monohydrate, magnesium stearate, corn 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 congenital defects: aplasia cutis, as manifested by scalp defects; esophageal atresia with tracheoesophageal fistula; and choanal atresia with absent/hypoplastic nipples, 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 the above congenital defects have been reported in offspring of patients treated with methimazole, it may be appropriate to use other agents in pregnant women requiring treatment for hyperthyroiodism.

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.

Drug Interactions

ANTICOAGULANTS (oral)
The activity of oral anticoagulants may be potentiated by anti-vitamin-K activity attributed to methimazole.

β-ADRENERGIC BLOCKING AGENTS
Hyperthyroidism may cause increased clearance of beta blockers with a high extraction ratio. A dose reduction of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.

DIGITALIS GLYCOSIDES
Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside

regimen become euthyroid; reduced dosage of digitalis glycosides may be required.

THEOPHYLLINE
Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

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

They are available in:

Bottles of 100	NDC 55567-080-18
Unit Dose Packages of 100	NDC 55567-080-06

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

They are available in:

Bottles of 100	NDC 55567-081-18
Unit Dose Packages of 100	NDC 55567-081-06

Methimazole Tablets, USP 20 mg - white to off-white, round, flat-faced, bevelled-edged tablets, scored with "EM" 20 on one side and plain on the other.

They are available in:

Bottles of 100	NDC 55567-126-18
Bottles of 1000	NDC 55567-126-35
Unit Dose Packages of 100	NDC 55567-126-06

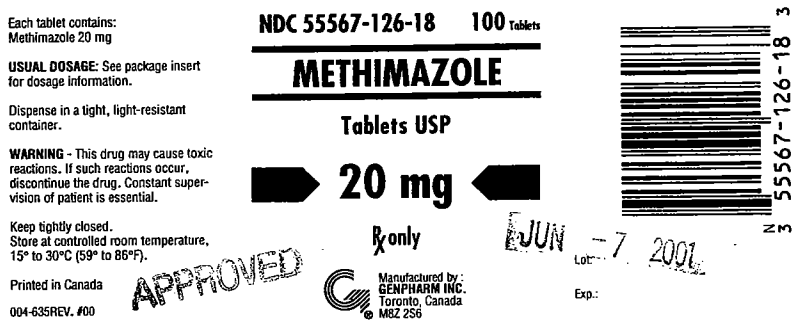
Store at controlled room temperature 15°-30°C (59°-86°F).

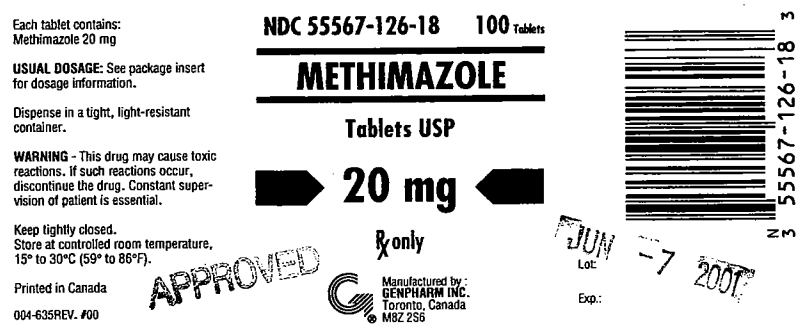
Bottle: Dispense in a tight, light-resistant container.

Unit Dose Package: To protect from light, product should remain in manufacturer's package until dispensed. If dispensed for out-patient use, dispense in a light-resistant container and an appropriate safety closure should be provided.

MANUFACTURED BY:
GENPHARM INC.
Toronto, Canada
M8Z 2S6

005-780 REV#02 March 2001


Each tablet contains:
Methimazole 20 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
004-635REV. #00
NDC 55567-126-18 100 Tablets
METHIMAZOLE
Tablets USP
20 mg
℞only
Manufactured by: GENPHARM INC. Toronto, Canada M8Z 2S6
APPROVED
JUN -7 2001
Lot:
Exp.:
N 3 55567-126-18 3


Each tablet contains:
Methimazole 20 mg
USUAL DOSAGE: See package insert for dosage information.
Dispense in a tight, light-resistant container.
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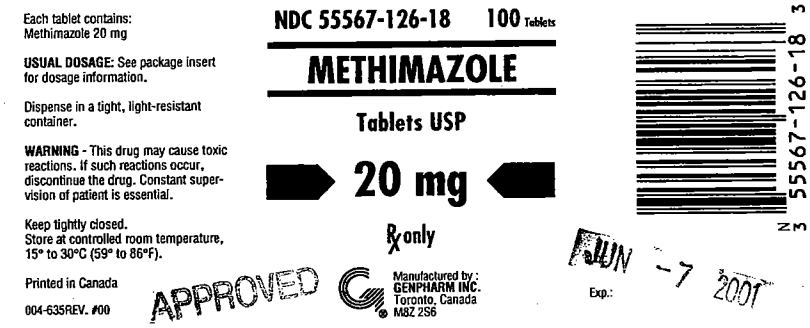
Each tablet contains:
Methimazole 20 mg
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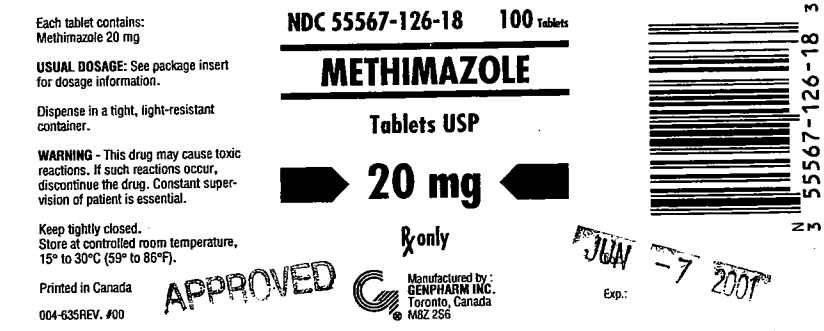
Each tablet contains:
Methimazole 20 mg
USUAL DOSAGE: See package insert for dosage information.
Dispense in a tight, light-resistant container.
WARNING - This drug may cause toxic reactions. If such reactions occur, discontinue the drug. Constant supervision of patient is essential.
Keep tightly closed.
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Printed in Canada
004-635REV. #00
NDC 55567-126-18 100 Tablets
METHIMAZOLE
Tablets USP
20 mg
℞only
Manufactured by: GENPHARM INC. Toronto, Canada M8Z 2S6
APPROVED
JUN -7 2001
Exp.:
N 3 55567-126-18 3

NDC 55567-126-06

METHIMAZOLE
Tablets USP
20 mg

Rx only

Manufactured by:
GENPHARM INC.
Toronto, Canada M8Z 2S6

100 Tablets
Unit Dose

JUN - 7 2001

10 Blister Strips
of 10 Tablets

NDC 55567-126-06

METHIMAZOLE
Tablets USP
20 mg
100 Tablets
Unit Dose

Each tablet contains: Methimazole 20 mg.

USUAL DOSAGE: See accompanying package insert.

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° to 86°F).

To protect from light, product should remain in manufacturer's package until dispensed. If dispensed for out-patient use, dispense in a light-resistant container and an appropriate safety closure should be provided.

N 3 55567-12606 0

NDC 55567-126-06

100 Tablets
Unit Dose

METHIMAZOLE
Tablets USP
20 mg

Rx only

GENPHARM INC.

10 Blister Strips
of 10 Tablets

NDC 55567-126-06

100 Tablets
Unit Dose

METHIMAZOLE
Tablets USP
20 mg

Rx only

GENPHARM INC.

10 Blister Strips
of 10 Tablets

NDC 55567-126-06

METHIMAZOLE
Tablets USP
20 mg

100 Tablets
Unit Dose

Lot No.:

Exp.:

007-877 Rev.#00

GENPHARM

Each tablet contains:
Methimazole 20 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.

004-638REV. #00

NDC 55567-126-35 1000 Tablets

METHIMAZOLE

Tablets USP

20 mg

℞ only

JUN -7 2001
APPROVED

Manufactured by :
GENPHARM INC.
Toronto, Canada
M8Z 2S6

Lot:
Exp.:

N 3 55567-126-35 0

Each tablet contains:
Methimazole 20 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.

004-638REV. #00

NDC 55567-126-35 1000 Tablets

METHIMAZOLE

Tablets USP

20 mg

℞ only

JUN -7 2001
APPROVED

Manufactured by :
GENPHARM INC.
Toronto, Canada
M8Z 2S6

Lot:
Exp.:

N 3 55567-126-35 0

METHIMAZOLE
TABLET, USP
20 mg
(L)XXXXXX Exp.:MMM YYYY
Mfg. By:
Genpharm Inc.
Toronto, Canada M8Z 2S6

METHIMAZOLE
TABLET, USP
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Toronto, Canada M8Z 2S6

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APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING #1

SUPPLEMENT

DRAFT & printer's proof

DATE OF REVIEW: February 15, 2001
ANDA #: 40-350/S-004
NAME OF FIRM: Genpharm Inc.
NAME OF DRUG: **Methimazole Tablets USP, 20 mg**
DATE OF SUBMISSION: Oct. 19, 2000

COMMENTS:

Container: 100s and 1000s - Satisfactory in printer's proof in the October 19, 2000 submission

Unit Dose: 10X10s - Satisfactory in draft in the October 19, 2000 submission

Unit Dose Carton: 10x10s - Satisfactory in printer's proof in the October 19, 2000 submission

Insert:

1. DESCRIPTION - Revise your inactive ingredient state to include the type of lactose and starch as seen in your composition statement "Lactose monohydrate and Corn starch.

2. HOW SUPPLIED-We note that the innovator's product is scored. Please cite for each of your product strengths whether your tablets are scored.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their insert labeling , then prepare and submit 12 final printed insert labeling and Unit dose labeling

NOTE TO CHEMIST: Draft Bulk container labels are present for your review. Please verify for me whether the 20 mg are scored. Thanks yes, they are scored. BL 3/7/01

FOR THE RECORD:

1. Review based on the labeling of Tapazole (Eli Lilly; methimazole, revised Oct 5, 1994 ; approved March 20, 1995.)
2. Supplement submitted for additional strength the 20 mg. A suitability petition was approved on Sept 9, 2000 Docket No: oop-1308CPI
3. Innovator markets only the 5 and 10 mg tabs they are scored. It appears that the 20 mg are scored(see section XI (2) page 1491 vol 4.4

cc: ANDA 40-350
Dup/Division File
HFD-613/APayne/JGrace (no cc:)
V:/firmsam/Genpharm/lets&rev/40350S004.na1
Review

APayne 02/15/01
JGrace 2/15/2001

REVIEW OF PROFESSIONAL LABELING #2

(minor)
SUPPLEMENT

FPL

DATE OF REVIEW: May 16, 2001
ANDA #: 40-350/S-004
NAME OF FIRM: Genpharm Inc.
NAME OF DRUG: **Methimazole Tablets USP, 20 mg**
DATE OF SUBMISSION: May 4, 2001

COMMENTS:

Container: (20 mg) 100s and 1000s - Satisfactory in FPL in the October 19, 2000 submission vol 4.1/

Unit Dose: (20 mg) 10s - Satisfactory in FPL in the May 4, 2001 submission vol 6.1

Unit Dose Carton: (20 mg) 10x10s - Satisfactory in FPL in the May 4, 2001 submission vol 6.1

Insert: - Satisfactory in FPL(#005-780 rev #02 March 2001) in the May 4, 2001 submission vol 6.1

RECOMMENDATIONS: Labels and labeling are satisfactory for approval.

NOTE TO CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Tapazole (NDA 7-517/S-022, Eli Lilly; methimazole, revised Oct 5, 1994 ; approved Jan 16, 2001)
2. Supplement submitted for additional strength the 20 mg. A suitability petition was approved on Sept 9, 2000 Docket No: oop-1308CPI
3. Innovator markets only the 5 and 10 mg tabs they are scored. It appears that the 20 mg are scored(see section XI (2) page 1491 vol 4.4

cc: ANDA 40-350
Dup/Division File
HFD-613/APayne/JGrace (no cc:)
V:/firmsam/Genpharm/lets&rev/40350S004.apl
Review

5/16/01

5/17/2001

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

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

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:
King & Spalding
Attn: Eugene Pfeifer
1730 Pennsylvania Avenue, N.W.
Washington , D.C.
Telephone: (202) 737-0500

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

5. **Supplement(s):** S-001, S-002, S-003, and S-004
6. **PROPRIETARY NAME:** None

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

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
S-001: New Strength;
S-002: Control Revision;
S-003: Packaging Addition; and
S-004: Label Revision

9. **AMENDMENTS AND OTHER DATES:**
Genpharm:
10/19/00 Submission of ANDA

FDA:
11/29/00 Bio review-acceptable (Vol. 4.1).
02/15/01 Labeling-Deficiencies (Vol. 4.1).

10. **PHARMACOLOGICAL CATEGORY:** Antihyperthyroid

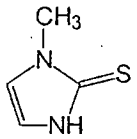
11. **Rx or OTC**: Rx

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: N/A
- Labeling review: Deficiency per 02/15/01
- Bio-review: Acceptable per 11/29/00
- Micro: N/A
- MV: Not required (USP DS/DP)
- NA Minor, labeling deficiencies.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
NA Minor.

19. **REVIEWER**: Bing Cai, Ph.D. **DATE COMPLETED**: 03/06/01 **DATE REVISED**:

Redacted 9

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:
King & Spalding
Attn: Eugene Pfeifer
1730 Pennsylvania Avenue, N.W.
Washington , D.C.
Telephone: (202) 737-0500

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

5. **Supplement(s):** S-001, S-002, S-003, and S-004
6. **PROPRIETARY NAME:** None

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

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
S-001: New Strength;
S-002: Control Revision;
S-003: Packaging Addition; and
S-004: Label Revision

9. **AMENDMENTS AND OTHER DATES:**

Genpharm:

10/19/00	Submission of Supplements
11/10/00	Certifications
11/16/00	Bio ESD
05/04/01	Minor Amendment

FDA:

11/29/00	Bio review-acceptable (Vol. 4.1).
02/15/01	Labeling-Deficiencies (Vol. 4.1).

03/22/01 NA, MINOR

10. **PHARMACOLOGICAL CATEGORY**: Antihyperthyroid

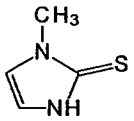
11. **Rx or OTC**: Rx

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: N/A
- Labeling review: Acceptable per 05/17/01
- Bio-review: Acceptable per 11/29/00
- Micro: N/A
- MV: Not required (USP DS/DP)
- Chemistry Approved

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Approved

19. **REVIEWER:**	**DATE COMPLETED:**	**DATE REVISED:**
Bing Cai, Ph.D.	05/23/01	

Redacted 4

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40350, SCQ001 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Methimazole 5 mg, 10 mg & 20 mg Tablets

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

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,

Dale P. Conner

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

Methimazole Tablet
20 mg (New Strength)

Genpharm Inc.
Wilmington, NC

ANDA 40-350, SCQ001
Reviewer: Lin-Whei Chuang
V:\FIRMSAM\GENPHARM\LTRS&REV\40350SD.000

Submission Date:
October 19, 2000

REVIEW OF A SUPPLEMENT CONTAINING A FASTING BIOEQUIVALENCE STUDY AND DISSOLUTION DATA FOR THE APPROVAL OF A HIGHER STRENGTH (20 MG)

Background:

1. The firm's methimazole 5 mg and 10 mg tablets were approved on 3/29/00 under this ANDA based on Tapazole^{R} 10 mg tablet by Eli Lilly and Co. (NDA #07517).

2. A Suitability Petition was approved on 9/9/00 for the firm to file an ANDA on the 20 mg strength based on Tapazole^{R} 10 mg tablet.

3. Currently, the RLD, Tapazole^{R} 10 mg tablet, is distributed exclusively by [redacted]

4. In this supplement the firm has conducted a fasting bioequivalence study and dissolution testing.

Formulation of Test Product:

Formulations of Genpharm's Methimazole Tablets			
	5 mg Tablet	10 mg Tablet	20 mg Tablet
	mg/Tablet		
Methimazole	5	10	20
Starch	[redacted]	[redacted]	[redacted]
Lactose Monohydrate	[redacted]	[redacted]	[redacted]
Talc	[redacted]	[redacted]	[redacted]
Magnesium Stearate	[redacted]	[redacted]	[redacted]

In vivo Bioavailability Study -- Fasting Subjects:

Objective:
To compare the single-dose bioavailability of Genpharm 1X20 mg methimazole tablets and [redacted] Tapazole® (methimazole 2X10 mg) tablets, under fasting conditions following an oral dose of 20 mg.

Sites, Dates, and Principal Investigator:
Clinical: [redacted]

2/8-10/00 (period 1)
2/15-17/00 (period 2)

Analytical: [redacted]

2/23-4/12/00

The maximal storage period for the study samples was 62 days.

Design and IRB:
A single-dose, randomized, 2-way crossover of the test drug and RLD under fasting conditions. The clinical protocol dated 1/21/00 and informed consent form dated 1/31/00 were approved by the Institute Review Board of [redacted] on 2/1/00.

Washout Period:
7 days

Subject Selection:
Thirty-two (30 plus 2 alternates) men (31 Caucasians and 1 Black) with 20-42 years of age, were selected according to criteria stated on pages 30-31 of the protocol (pages 100-101 of vol. 1/3).

Restrictions:
Restrictions were instructed to all subjects as stated in page 31 of the protocol (page 1101 of vol. 1/3).

Treatments:
After an overnight fast, in the morning of 2/9/00, subjects received one of the following drug treatments, according to the randomly assigned sequence (AB for subjects #3, 5, 6, 9, 12, 14,

15, 17, 18, 20, 21, 25, 26, 28, 29, 31; and BA for the rest of subjects) with 240 mL of water:

Treatment A - Test Drug: One methimazole 20 mg tablet, Genpharm Inc., lot #AC312, manufactured 3/31/98, assay potency 101.4%, executive batch size ——— tablets.

Treatment B - Reference Drug: Two Tapazol® 10 mg tablets, Eli Lilly lot #3MJ29M, assay potency 99.9%, expires 6/1/01.

After a 7-day washout period, in the morning of 2/16/00, subjects received the alternative treatment.

Post-dose Procedure:
The unused drug supplies were retained at the clinical site. For the 4 hours post-dose, subjects remained fasted, ambulatory, and not smoking. Water was not allowed from 1 hour pre-dose to 1 hour post-dose except for that given with the study drug.

Blood samples were drawn into EDTA-containing tubes at pre-dose and at 0.083, 0.167, 0.25, 0.33, 0..417, 0.5, 0.67, 0.83, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 36 hours post-dose. Plasma samples were prepared and stored at -22°C pending analysis.

Among the tests of serum chemistry conducted during screening, the SGOT and SGPT tests were repeated following the completion of the study and the TSH test was repeated 4 weeks after the last dose.

Analytical Method -- ***Not Releasable through FOI:***

[redacted]

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

Results:

Drop-out:
Of the 32 subjects enrolled, subject #17 elected to withdraw from the study after period 1 due to personal reason.

Protocol Deviation
No significant deviations were reported.

Adverse Event:

	Total Events	Events Possibly Treatment-Related
Treatment A	3	0
Treatment B	5	1 (headache)

Post-Study Laboratory Test:
Results of all serum chemistry tests including SGOT, SGPT and TSH were either within normal range or judged to be not clinically significant.

Plasma Concentration and Pharmacokinetic Analysis
A total of 1199 plasma samples from 30 subjects (#1-16 & #18-31) were assayed for methimazole. One plasma sample was not received at the analytical site, subject #20, period 1, treatment A, 0.083 hour, which however was not at the Tmax nor adjacent to the Tmax therefore should not affect the outcome of the study. No samples were re-assayed due to pharmacokinetic anomaly.

The mean plasma concentrations of methimazole at each sampling time point and the mean pharmacokinetic parameters after both treatments are presented in Figure 1 and Tables 3-4.

FIG 1: PLASMA METHIMAZOLE LEVELS

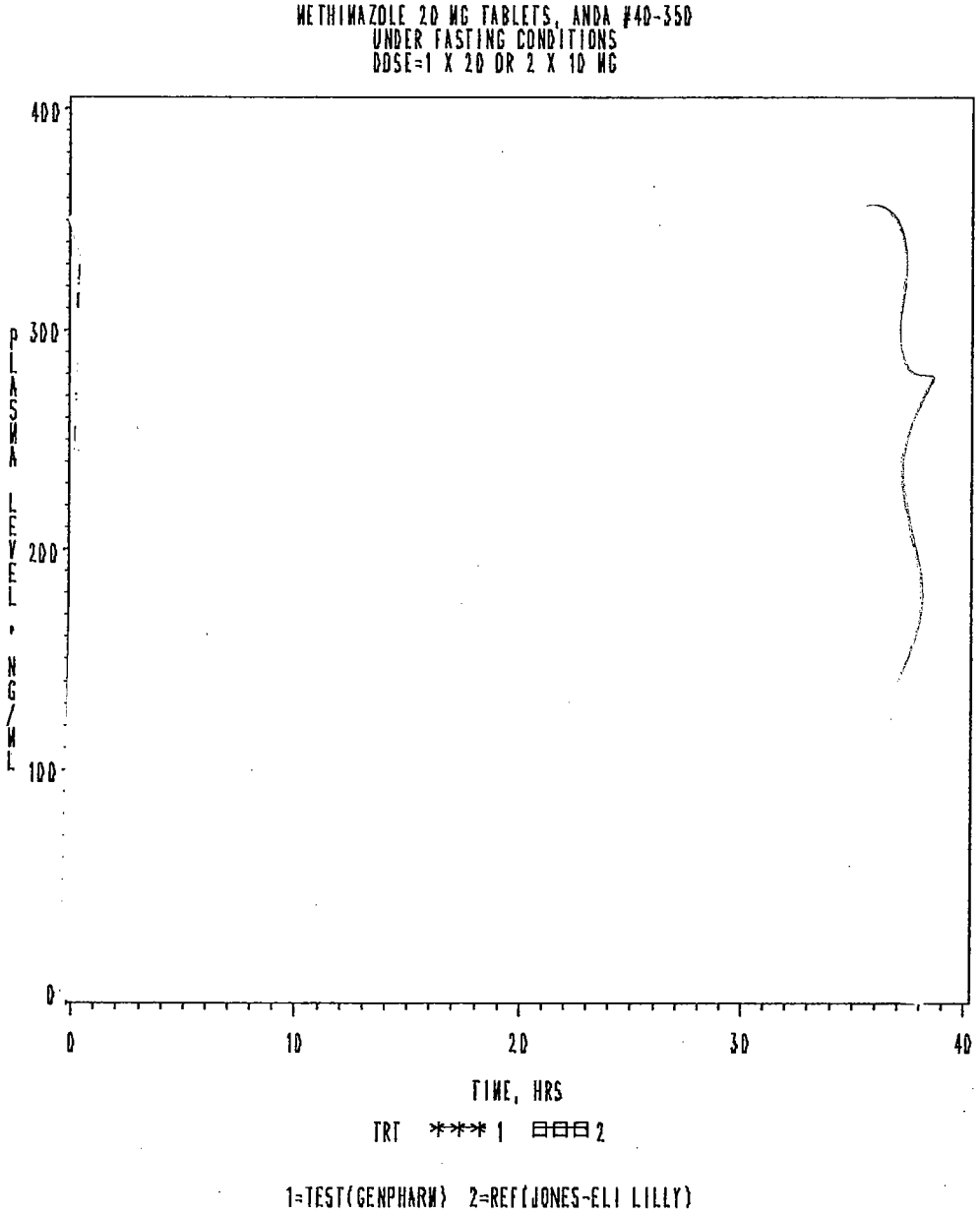

TABLE 3: ARITHMETIC MEAN OF PLASMA METHIMAZOLE LEVELS (NG/ML) AND RATIOS OF MEANS (20 MG UNDER FASTING CONDITIONS, N=30 EXCEPT WHEEN INDICATED)

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
0	0.000	0.000	0.000	0.000	.
0.083	4.163a	9.610	3.272	14.398	1.272
0.167	41.125	49.759	27.068	36.742	1.519
0.25	152.108	140.461	121.241	107.403	1.255
0.33	269.535	180.981	252.841	180.103	1.066
0.417	322.333	167.563	313.246	175.552	1.029
0.5	322.058	134.149	326.569	107.756	0.986
0.67	347.811	95.426	343.342	81.207	1.013
0.83	341.398	68.682	342.034	58.438	0.998
1	338.454	61.399	331.225	52.015	1.022
1.5	321.986	39.482	311.311	45.221	1.034
2	299.432	33.446	291.084	40.444	1.029
2.5	280.086	37.426	276.762	39.025	1.012
3	267.166	33.138	262.457	33.966	1.018
4	241.048	31.332	238.827	32.913	1.009
6	193.165	27.124	189.520	30.732	1.019
8	146.904	23.236	146.782	25.168	1.001
12	86.259	19.885	84.256	17.926	1.024
24	22.222	9.555	20.715	7.562	1.073
36	5.062	4.040	4.737	3.134	1.069

a = (N=29)

TABLE 4: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS AND RATIOS OF MEANS (20 MG UNDER FASTING CONDITIONS, N=30)

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI (NG*HR/ML)	3210.70	516.41	3135.17	506.24	1.02
AUCT (NG*HR/ML)	3141.80	501.53	3076.70	497.11	1.02
CMAX (NG/ML)	407.43	104.11	413.26	137.87	0.99
KE	0.12	0.02	0.12	0.02	1.00
LAUCI	3171.03a	0.16c	3096.58a	0.16c	1.02b
LAUCT	3103.23a	0.16c	3038.56a	0.16c	1.02b
LCMAX	395.81a	0.24c	394.99a	0.29c	1.00b
THALF	5.81	0.96	5.78	0.80	1.01
TMAX (HR)	0.73	0.41	0.76	0.38	0.96

a = GEOMETRIC MEAN, b = RATIO OF GEOMETRIC MEANS,
c = SD OF LOG-TRANFORMED PARAMETERS

Means of Ratios of Test to Reference Products:

Parameters	N	Mean	Std Dev	Minimum	Maximum
AUCT	30	1.02	0.08	0.87	1.17
AUCI	30	1.03	0.08	0.87	1.17
CMAX	30	1.02	0.18	0.59	1.40
TMAX	30	1.09	0.63	0.30	3.00
KE	30	1.00	0.07	0.87	1.11
THALF	30	1.00	0.07	0.90	1.15

Means of Ratios of AUCT/AUCI:

Treatment A: 0.98 (0.96-0.99)
Treatment B: 0.98 (0.96-0.99)

Statistical Analysis:
ANOVA was performed by the firm on the log-transformed AUCT, AUCI and Cmax. The statistical model contained main effects of sequence, subject within sequence, period and treatment. Sequence effects were tested against the type III mean square term for subject within sequence. All other main effects were tested against the mean square error term. No significant effects were detected for any of the pharmacokinetic parameter.

The reviewer conducted her own ANOVA on the non-transformed and log-transformed pharmacokinetic parameters. The LS means, ratios of these means and the 90% confidence intervals of test t versus reference products are presented in Table 5. The firm's results are identical to those in Table 5.

Table 5: LS Means (LSM) and 90% Confidence Intervals (CI)

	TEST LSM	REF. LSM	TEST/REF.	90% CI
PARAMETER				
AUCI (NG*HR/ML)	3210.70	3135.17	1.02	100.04 - 104.78
AUCT (NG*HR/ML)	3141.80	3076.70	1.02	99.75 - 104.48
CMAX (NG/ML)	407.43	413.26	0.99	91.42 - 105.76
LAUCI	3171.03a	3096.58a	1.02b	100.02 - 104.84
LAUCT	3103.23a	3038.56a	1.02b	99.74 - 104.57
LCMAX	395.81a	394.99a	1.00b	94.39 - 106.39

a = Geometric LS Mean, b = Ratio of Geometric LS Means,

Comments on Results of Bioequivalence Study:

1. The computation of pharmacokinetic parameters and 90% confidence intervals conducted by the firm has been confirmed by the reviewer.

2. The results of this fasting bioequivalence study are acceptable

Dissolution:

Following dissolution data were submitted by the firm:

Table 6- In Vitro Dissolution Testing

Drug (Generic Name): Methimazole
Dosage Form: Tablets
Dose Strength: 20 mg
ANDA No.: 40-350
Firm: Genpharm Inc.
Submission Date: 10/19/00

I. Conditions for Dissolution Testing:

USP 24 Apparatus: Basket RPM: 100 No. Units Tested: 12
Medium: water Volume: 500 mL
Tolerance: NLT 80%(Q) in 30 minutes
Reference Drug: Tapazole^{R} Tablets (Eli Lilly)
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times (minute)	Test Product Lot #AC312 Strength (mg): 20			Reference Product Lot #3MJ29M. Strength (mg): 10		
	Mean %	Range	%CV	Mean %	Range	%CV
5	98.6	[redacted]	1.6	49.2	[redacted]	22.7
10	101.4	[redacted]	2.4	84.2	[redacted]	9.3
20	101.7	[redacted]	1.8	98.5	[redacted]	2.7
30	101.4	[redacted]	2.0	100.7	[redacted]	1.2

Comment on Dissolution Data:

Methimazole tablets are USP product. The dissolution method and specification conducted by the firm are in accordance with those published in USP 24. The dissolution results are acceptable.

Recommendation:

1. The bioavailability study conducted by Genpharm Inc. on its methimazole 20 mg tablet, Lot #AC312, comparing it to Tapazole^{R} 10 mg tablet, lot #3MJ29M, manufactured by Eli Lilly & Co. Company, has been found acceptable by the

Division of Bioequivalence. The study demonstrated that Genpharm's methimazole 20 mg tablet is similarly bioavailable to the reference product, Tapazole^{R} 10 mg Tablet manufactured by Eli Lilly & Co. Company, when administered under fasting conditions at 20 mg dose.

2. The dissolution testing conducted by Genpharm Inc. on its methimazole 20 mg tablet, Lot #AC312, comparing it to Tapazole^{R} 10 mg tablet, lot #3MJ29M, manufactured by Eli Lilly & Co. Company, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 500 mL of water at 37° C using USP 24 apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

   Not less than 80% (Q) of the labeled amount of methimazole in the dosage form is dissolved in 30 minutes.

Lin-Whei Chuang 11/28/00

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 11/28/2000

Concur Dale P. Conner Date: 11/29/00
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #40-350 / SCQ001
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Lin-Whei Chuang

V:\FIRMSAM\GENPHARM\LTRS&REV\40350SD.000

Endorsements: (Final with Dates)
HFD-652/ L. Chuang LWC 11/28/00
HFD-652/ Y. Huang YH 11/28/2000
HFD-650/ D. Conner DC 11/29/00
HFD-652/ K. Scardina ES 11/29/00

BIOEQUIVALENCY - ACCEPTABLE submission date: 10/19/00

1. **FASTING STUDY** (STF) clr Strength: 20 mg
Outcome: AC
Clinical:
Analytical:

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-350, SCQ001 SPONSOR : Genpharm Inc.

DRUG AND DOSAGE FORM : **Methimazole Tablets**

STRENGTHS : 20 mg (New Strength)

TYPES OF STUDY : Fasting *In Vivo* Bioequivalence Study

CLINICAL STUDY SITE : [redacted]

ANALYTICAL SITE : [redacted]

STUDY SUMMARY : Acceptable

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Lin-Whei Chuang BRANCH : I

INITIAL : LW C DATE : 11/28/00

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : [signature] DATE : 11/28/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [signature] DATE : 11/29/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40350, SCQ001 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Methimazole 5 mg, 10 mg & 20 mg Tablets

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

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,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

ADMINISTRATIVE DOCUMENTS

Patent and Exclusivity Search Results from query on 007517 002.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

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Search results from the "Rx" table for query on "007517."

Active Ingredient:	METHIMAZOLE
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	TAPAZOLE
Applicant:	LILLY
Strength:	5MG
Application Number:	007517
Product Number:	002
Approval Date:	Approved prior to Jan 1, 1982
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	METHIMAZOLE
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	TAPAZOLE
Applicant:	LILLY
Strength:	10MG
Application Number:	007517
Product Number:	004
Approval Date:	Approved prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	Click Here

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-350/S-001; S-002; S-003; S-004

CORRESPONDENCE

GENPHARM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

NDA SUPPL AMENDMENT

SCQ-001
SCS-002
SCA-003
SL-004
AM

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

Dear Sir/Madam:

Please find enclosed Genpharm's response to the deficiency letter dated March 22, 2001 from FDA.

We have enclosed: one (1) archival copy and one (1) review copy of the application in accordance with 21 CFR § 314.96.

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. Eugene Pfeifer of King & Spalding, at (202)-737-0500.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 07 2001
OGD

Yours sincerely,

Dr. Bonnie Southorn
Director, Core Technical Documentation and Submissions
GENPHARM INC.

MAY 04 2001
Date

ANDA 40-350/S-001,S-002,S-003,S-004

APR 12 2001

King & Spalding
U.S. Agent for: Genpharm Inc.
Attention: Eugene Pfeifer
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-4706

Dear Sir:

This is in reference to your supplemental new drug applications dated October 19, 2000, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Methimazole Tablets USP, 5 mg and 10 mg.

The supplemental applications provide for a new strength (S-001), associated control revisions (S-002), associated packaging (S-003), and associated labeling (S-004).

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reason:

1. Labeling Deficiencies:

COMMENTS:

Container: 100s and 1000s - Satisfactory in printer's proof in the October 19, 2000 submission.

Unit Dose: 10X10s - Satisfactory in draft in the October 19, 2000 submission.

Unit Dose Carton: 10x10s - Satisfactory in printer's proof in the October 19, 2000 submission.

Insert:

1. DESCRIPTION - Revise your inactive ingredient state to include the type of lactose and starch as seen in your composition statement "Lactose monohydrate and Corn starch".

2. HOW SUPPLIED-We note that the innovator's product is scored. Please cite for each of your product strengths whether your tablets are scored.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their insert labeling, then prepare and submit 12 final printed insert labeling and Unit dose labeling

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental applications. Your amendment should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all the deficiencies have been addressed. The response to this letter will be considered a Minor amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving the supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

Kenneth P. Trunkroary, for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

GENPHARM

SUITABILITY

NDA NO. _____ REF NO. SCQ 001
NDA SUPPL FOR New Strength (BIO)

NDA NO. _____ REF NO. SCS 002
NDA SUPPL FOR Control test

NDA NO. _____ REF NO. SEA 003
NDA SUPPL FOR Package Add

OCT 19 2000

SUPPLEMENT

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

NDA NO. _____ REF NO. SLO04
NDA SUPPL FOR Label test

Re: Supplement to approved ANDA #40-350
Methimazole Tablets
5 mg and 10 mg

We are pleased at this time to submit a Supplement to our approved Abbreviated New Drug Application, #40-350, for our product Methimazole Tablets USP, 5 mg and 10 mg.

The purpose of this supplemental application is to provide for an additional strength, a 20 mg tablet. This supplement to an ANDA for an additional strength is based on the approval of a petition pursuant to 21 U.S.C §505(j)(2)(c) and 21 CFR 314.93 that requests a change from the listed drug Tapazole Tablets 5 and 10 mg. The ANDA Suitability Petition was submitted under **Docket No: 00P-1308/CP1** and approved on **September 9, 2000.** A copy of the FDA letter approving the petition is provided in Section II of the submission.

Methimazole Tablets 20 mg are manufactured at the same site and under the same controls as Methimazole Tablets 5 mg and 10 mg which are approved under ANDA #40-350. Methimazole Tablets 20 mg are manufactured with active ingredient from the manufacturer approved in ANDA #40-350, CU

Information that was presented in the original approved ANDA 40-350 has not been presented in this supplemental submission if it is common to all strengths of the product. This supplemental submission is made up of new documents relevant to the 20 mg tablet, or documents that have been updated from the time of the original approval. Please refer to the "Executive Summary - Introduction to this Supplement" for an overview of the basis of the submission. This application has been presented in the same format as the original application and contains all sections required in an ANDA.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.94. 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.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 25 2000
OGD

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

The following number of volumes have been presented:

Archival Copy (Blue)	4 volumes
Review Copy (Red)	1 volumes
Review Copy (Orange)	3 volumes
Field Copy (Burgundy)	1 volumes
Analytical Methods (Blue)	1 volume (2 copies)

This submission does not contain an electronic submission ESD (BA/BE EVA). It will be sent in the allowable 30 day timeframe from the date of submission of the hardcopy application.

We trust the information submitted is sufficient for this Supplemental Application 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 to the attention of the undersigned or you may contact our U.S. agent King & Spalding.

Yours sincerely

Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

Oct 19/00
(date)