

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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February 14, 2000

OVERNIGHT COURIER 2/14/00

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

1614 00 JUN 27 00:08

CITIZEN PETITION

Lachman Consultant Services, Inc. (LCS) submits this petition in quadruplicate, pursuant to 21 CFR 10.20 and 10.30, under Section 505 (j)(2)(C) of the Federal Food, Drug and Cosmetic Act to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application may be submitted for Methimazole Tablets USP, 20 mg.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application may be submitted for Methimazole Tablets, USP, 20 mg. The listed drug product upon which this petition is based is Tapazole® (Methimazole Tablets, USP) 10 mg (Eli Lilly and Company). LCS seeks a change in the dosage strength from that of the listed drug to permit a 20 mg tablet.

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a new drug that differs in dosage strength from a listed drug provided the FDA has approved a petition that proposed the filing of such an application. This petition involves a change in the dosage strength for the proposed drug from that of the listed drug. The listed drug on which this petition is based is Tapazole® Tablets (Methimazole Tablets, USP) manufactured by Eli Lilly and Company. See listing on page 3-222 of the Nineteenth Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Attachment 1)).

There should be no questions of safety and efficacy regarding the requested change in strength. Currently, Methimazole Tablets, USP is approved in 5 and 10 mg strengths and is indicated in the medical treatment of hyperthyroidism. The approved reference listed drug product's labeling cites the initial total daily dosage of 15 mg (5 mg given in 3 equal doses at 8-hour intervals) for mild hyperthyroidism, 30-40 mg for moderately severe hyperthyroidism, and a daily dose of 60 mg is recommended for severe hyperthyroidism. It is clear that doses of 20 mg divided into 3 doses at 8-hour intervals (or three 20 mg doses), the proposed strength that is the subject of this petition, is clearly contemplated and addressed in the approved labeling of the reference drug product. Additionally, for patients experiencing severe hyperthyroidism, a 20 mg tablet taken three times

00P-1375

CPI

daily would appear to offer a more convenient dosing regimen (one tablet 3 times per day rather than 2 tablets 3 times per day) than that currently available for the reference listed drug.

The uses, dosages, and indications for the proposed product are the same as those for Tapazole® Tablets, the listed drug product. Labeling of the proposed product will be the same as that of the listed-drug product with the exception of the introduction of the 20 mg strength in the description and how supplied section of the labeling. Copies of the reference-listed drug labeling and draft labeling for the proposed Methimazole Tablets, USP are enclosed for your reference.

C. Environmental Impact

An environmental assessment of the action requested in this petition qualifies for a categorical exclusion under 21 CFR 25.31. Therefore, an environmental assessment is not required for the requested action.

D. Economic Impact

Pursuant to 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner. LCS will promptly provide such information if so requested.

E. Certification

The petitioner certifies that, to its best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,



Robert W. Pollock
Vice President

RWP/db

- Attachments:
1. *Listing of Tapazole® Tablets (5 or 10 mg) page 3-222 of the Nineteenth Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations*
 2. *Proposed package insert-draft Methimazole Tablets, USP (20 mg)*
 3. *Package insert for Tapazole® Tablets*

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LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
February 14, 2000

Attachment 1

**Listing of Tapazole® Tablets (5 or 10 mg) page 3-222 of the Nineteenth Edition
of the Approved Drug Products with Therapeutic Equivalence Evaluations**

PRESCRIPTION DRUG PRODUCT LIST

3-222

METHAZOLAMIDE

TABLET; ORAL
METHAZOLAMIDE
AB APPLIED ANAL 25MG N40011 001
 JUL 17, 1997
AB 50MG N40011 002
 JUL 17, 1997
AB COPLEY PHARM 25MG N40001 001
 JUN 30, 1993
AB 50MG N40001 002
 JUN 30, 1993
AB GENEVA PHARMS 25MG N40036 001
 JUN 30, 1993
AB 50MG N40036 002
 JUN 30, 1993
AB INVAMED 25MG N40102 001
 AUG 28, 1996
AB 50MG N40102 002
 AUG 28, 1996
AB MIKART 25MG N40062 001
 JAN 27, 1994
AB 50MG N40062 002
 JAN 27, 1994
AB NEPTAZANE
 LEADERLE 25MG N11721 002
 NOV 25, 1991
AB + 50MG N11721 001

METHENAMINE HIPPURATE

TABLET; ORAL
HIPREX
AB + HOECHST MARION RSSL 1GM N17681 001
AB UREX
 3M 1GM N16151 001

METHICILLIN SODIUM

INJECTABLE; INJECTION
 STAPHICILLIN
 + APOTHECON EQ 900MG BASE/VIAL N61449 001
 + EQ 3.6GM BASE/VIAL N61449 002
 + EQ 5.4GM BASE/VIAL N61449 003

METHIMAZOLE

TABLET; ORAL
 TAPAZOLE
 LILLY 5MG N07517 002
 + 10MG N07517 004

METHOCARBAMOL

INJECTABLE; INJECTION
METHOCARBAMOL
AP STERIS 100MG/ML N86459 001
AP + ROBINS AH 100MG/ML N11790 001

TABLET; ORAL
METHOCARBAMOL
AA CHELSEA LABS 500MG N85180 001
AA 750MG N85192 001
AA DANBURY PHARMA 500MG N84277 001
AA 750MG N84276 002
AA EON 500MG N87283 001
AA 750MG N87282 001
AA GENEVA PHARMS 500MG N84616 001
AA 750MG N84615 001
AA GLOBAL PHARM 500MG N84927 001
AA 750MG N84928 001
AA LANNETT 750MG N84756 001
AA LEADERLE 500MG N85961 001
AA 750MG N85963 001
AA NYLOS 750MG N85033 001
AA PAR PHARM 500MG N86989 001
AA 750MG N86988 001
AA SUPERPHARM 500MG N87589 001
AA 750MG N87590 001
AA TABLICAPS 500MG N84846 001
AA WEST WARD 500MG N85159 001
AA 750MG N85123 001
AA ROBAXIN
AA + ROBINS AH 500MG N11011 004
AA + ROBINS AH ROBAXIN-750
750MG N11011 006

METHOCARBAMOL; *MULTIPLE*
 SEE ASPIRIN; METHOCARBAMOL

LACHMAN CONSULTANT SERVICES, INC.

Westbury, NY 11590

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
February 14, 2000

Attachment 2

Proposed Package Insert (draft) for Methimazole Tablets, USP (20 mg)

METHIMAZOLE TABLETS, USP

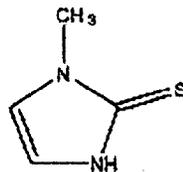
Rx only

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-membered 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, magnesium stearate, starch, and talc.

The molecular weight is 114.17, and the molecular formula is $\text{C}_4\text{H}_6\text{N}_2\text{S}$. 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.

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/mm³), 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 ½ 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" on one side and plain on the other.

5

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" on one side and plain on the other.

10

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

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

20

They are available as follows:

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

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



Manufactured by:
GENPHARM INC.
Toronto, Canada
MBZ 238
1-800-661-7134

Printed in Canada.

xxx-xxx (Item Number)

Rev # 00

January, 2000

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
February 14, 2000

Attachment 3

Package Insert for Tapazole® Tablets

laboratory tests such as serum T₄, serum T₃, and the free thyroxine index will be elevated during the period of over-... and the hallmark is a clearly suppressed serum TSH... Complications as a result of the induced hypermeta-... may include cardiac failure and death due to ar-... or failure.

TREATMENT OF OVERDOSAGE—Dosage should be re-duced or therapy temporarily discontinued if signs and symptoms of overdosage appear. Treatment may be reinsti-tuted at a lower dosage.

Management of acute massive thyroid hormone overdosage is aimed at reducing gastrointestinal absorption of the drugs and counteracting central and peripheral effects, mainly of increased sympathetic activity. Vomiting may be in-duced initially if further gastrointestinal absorption can be prevented provided there are no contraindi-cations such as coma, convulsions, or loss of the gag reflex. Treatment is mainly symptomatic and supportive. Oxygen should be administered and ventilation maintained. Cardiac arrhythmias may be indicated if congestive heart failure de-velops. Measures to control fever, hypoglycemia, or fluid loss should be instituted if needed. Antiadrenergic agents, par-ticularly propranolol, have been used advantageously in the treatment of increased sympathetic activity. Propranolol may be administered intravenously at a dosage of 1 to 3 mg every 4 to 10 minute period or orally, 80 to 160 mg/day, espe-cially when no contraindications exist for its use.

DOSE AND ADMINISTRATION

Primary Hypothyroidism—The goal of therapy in primary hypothyroidism should be the restoration of euthyroidism as judged by clinical response and confirmed by appropriate laboratory tests such as serum thyroxine (T₄), serum triiodothyronine (T₃), free thyroxine index and serum TSH; the principal measure in primary hypothyroidism is the serum T₄ level. The age and general condition of the patient, the severity and duration of hypothyroid symptoms, and whether or not the serum TSH level remains high or has some normal determine the starting dose of LEVOXYL. The rate of incremental dosage increase leading to a fi-nal maintenance dosage.

Otherwise healthy adults with primary hypothyroidism, a recommended initial dosage of LEVOXYL is 25 to 100 (0.025 to 0.1 mg) daily, while the predicted full main-tenance dose of 100 to 200 mcg (0.1 to 0.2 mg) daily may be achieved in several months.

In the elderly patient with primary hypothyroidism, partic-ularly in those with long-standing or severe primary hypo-thyroidism or with evidence of cardiovascular dysfunction, an initial dose of LEVOXYL may be as little as 12.5 mcg (0.0125 mg) per day; incremental increases of 25 mcg (0.025 mg) per day at 4 to 6 week intervals may be instituted de-pending on patient response. It is the physician's judgement as to the severity of the disease and close observation of pa-tient response and of the serum TSH level which determine the rate and extent of dosage increase.

When the serum TSH level in those with primary hypothy-roidism has fallen to the normal reference range during LEVOXYL treatment and the serum TSH concentration has been stable at this level for 4 to 8 weeks, the daily dose be-comes less than the maintenance dose. To monitor the ad-justment of this dose and patient compliance, periodic assess-ment of the serum TSH level should be done. The aim is the maintenance of the serum TSH level in the normal refer-ence range. There are no data showing the optimum fre-quency of measurement of serum TSH concentration in this situation but common practice is 1 to 3 times per year; there is reason to suspect poor compliance with therapy or other potential problems, the serum TSH measurement should be done more often, even when the dose of oral T₄ is maintained.

Myxedema Hypothyroidism—Sometimes referred to as "myx-edema," far-advanced hypothyroidism is an uncommon but dangerous and potentially lethal state. Often precipi-tated by another event, such as infection or injury, in an al-ready hypothyroid patient and often characterized by hypo-tension and somnolence or actual coma, severe hypothy-roidism is a medical emergency. Other characteristics are bradycardia, electrolyte abnormalities such as hyponatremia, respiratory failure with CO₂ retention, and hypotension. The principal treatment initially is aimed at supportive therapy, and correction of non-thyroid abnormalities such as abnormal electrolyte values or cardiac arrhythmias. Glu-cocorticoid therapy is often given, although there are no data showing clear benefit. In addition, replacement ther-apy with levothyroxine is essential. While oral T₄ appears to be absorbed in such patients, there are no data showing controlled trial whether it is better to give the L-T₄ by nasogastric tube, or parenterally. Nevertheless, the preference is to give the L-T₄ parenterally. Similarly, there is no consensus on the dose of L-T₄ to be used; some pre-fer to replace the entire deficiency of circu-lating T₄ (often 400 to 600 mcg, usually parenterally, as a bolus given over a few hours) while other physicians prefer to begin with smaller doses, e.g., 75 to 150 mcg,

(0.075-0.15 mg) given by mouth, if possible, or parenterally if not. Further dosing of L-T₄ depends on patient response which in turn requires intensive monitoring for at least a few days. The total daily dose of L-T₄ given after the initial dose should in general not exceed the daily dose required previously by the patient or the average daily dose taken by similar patients. Clinical judgement is a major determinant of the details of treatment because laboratory results will usually not be available initially.

Secondary Hypothyroidism—Hypothyroidism due to pitui-tary or hypothalamic disease, or secondary hypothyroidism, is uncommon; the vast majority of hypothyroid patients have primary hypothyroidism. Secondary hypothyroidism is suspected whenever there is known hypothalamic or pitui-tary disease, such as pituitary tumor or diabetes insipidus; it is characterized by a low serum concentration of total T₄ or free T₄ without a clearly raised serum TSH concentra-tion; the serum TSH level may be slightly raised, in the refer-ence range, or low. The serum TSH level cannot be used to monitor the dosage of LEVOXYL as it is in primary hypo-thyroidism. The initial dose of LEVOXYL should be chosen as it is in the primary hypothyroidism, observing the same guidelines and precautions (see **Primary Hypothyroidism**). Further dose increases, if any, are based on the clinical re-sponse using clinical judgement and measurement of serum total or free T₄.

Suppression of Pituitary Secretion of TSH—In selected pa-tients with goiter, thyroid nodules, or papillary or follicular thyroid cancer, LEVOXYL can be used in an attempt to in-hibit growth or prevent re-growth of the abnormal thyroid tissue; the overall management may include other therapies such as surgery or radioactive iodine. The suppressive ac-tion of LEVOXYL is based on the known ability of oral T₄ to suppress pituitary secretion of TSH even when patients are initially euthyroid (a hypothyroid person with any of the above conditions should be treated with LEVOXYL in any case for the hypothyroidism). Because most persons with these conditions are euthyroid and so have a normal serum TSH concentration, the goal of LEVOXYL therapy is to sup-press the serum TSH level to below the reference range. In so doing, some patients with these conditions may have an inhibition of further growth of the abnormal thyroid tissue. Because various clinical trials have reached different con-clusions on the efficacy of oral T₄ in the treatment of thyroid nodules or goiter and there are no controlled trials on its use in papillary or follicular thyroid cancer or on the degree to which the serum TSH level needs to be suppressed, the use of LEVOXYL in these conditions needs to be individualized; continued use depends on the clinical response balanced against the possibility of induced hyperthyroidism. In gen-eral, the suppression of serum TSH concentration should be to the level of 0.1 to 0.2 mU/L although some prefer to sup-press the serum TSH concentration to less than 0.1 mU/L in patients with differentiated thyroid carcinoma.

Pediatric Hypothyroidism—In infants and children there is a great urgency to achieve full thyroid replacement because of the critical importance of thyroid hormone in sustaining growth and maturation as well as development of the brain and intellectual function. Despite the smaller body size, the dosage needed to sustain a full rate of growth, development and general thriving is higher in the child than in the adult. The recommended daily replacement dosage of L-thyroxine in childhood is: 0-6 months: 8-10 mcg/kg; 6-12 months: 6-8 mcg/kg; 1-5 years: 5-6 mg/kg; 6-12 years: 4-5 mcg/kg of body weight daily.

HOW SUPPLIED

- LEVOXYL (L-thyroxine) tablets are supplied as oval, color-coded, potency marked tablets in 12 strengths:
- 25 mcg-Orange:**
Bottles of 100, NDC 0689-1117-01
Bottles of 1000, NDC 0689-1117-10
Unit dose cartons of 100, NDC 0689-1117-05
- 50 mcg-White:**
Bottles of 100, NDC 0689-1118-01
Bottles of 1000, NDC 0689-1118-10
Unit dose cartons of 100, NDC 0689-1118-05
- 75 mcg-Purple:**
Bottles of 100, NDC 0689-1119-01
Bottles of 1000, NDC 0689-1119-10
Unit dose cartons of 100, NDC 0689-1119-05
- 88 mcg-Olive:**
Bottles of 100, NDC 0689-1132-01
Bottles of 1000, NDC 0689-1132-10
- 100 mcg-Yellow:**
Bottles of 100, NDC 0689-1110-01
Bottles of 1000, NDC 0689-1110-10
Unit dose cartons of 100, NDC 0689-1110-05
- 112 mcg-Rose:**
Bottles of 100, NDC 0689-1130-01
Bottles of 1000, NDC 0689-1130-10
- 125 mcg-Brown:**
Bottles of 100, NDC 0689-1120-01
Bottles of 1000, NDC 0689-1120-10
Unit dose cartons of 100, NDC 0689-1120-05

- 137 mcg-Dark Blue:**
Bottles of 100, NDC 0689-1135-01
Bottles of 1000, NDC 0689-1135-10
- 150 mcg-Blue:**
Bottles of 100, NDC 0689-1111-01
Bottles of 1000, NDC 0689-1111-10
Unit dose cartons of 100, NDC 0689-1111-05
- 175 mcg-Turquoise:**
Bottles of 100, NDC 0689-1122-01
Bottles of 1000, NDC 0689-1122-10
- 200 mcg-Pink:**
Bottles of 100, NDC 0689-1112-01
Bottles of 1000, NDC 0689-1112-10
Unit dose cartons of 100, NDC 0689-1112-05
- 300 mcg-Green:**
Bottles of 100, NDC 0689-1121-01
Bottles of 1000, NDC 0689-1121-10
Store at controlled room temperature 15°-30°C (59°-86°F)
Caution: Federal (USA) law prohibits dispensing without a prescription.
JONES MEDICAL INDUSTRIES, INC.
1945 Craig Road
ST. LOUIS, MO 63146
(NASDAQ: JMED)
800-525-8466
Revised May 1996
Shown in Product Identification Guide, page 318

**TABLETS
TAPAZOLE®
METHIMAZOLE TABLETS, USP**

DESCRIPTION

Tapazole® (Methimazole Tablets, USP) (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-membered ring. Each tablet contains 5 or 10 mg (43.8 or 87.6 pmol) methimazole, an orally administered antithyroid drug. Each tablet also contains lactose, magnesium stearate, starch, and talc. The molecular weight is 114.16, and the empirical formula is C₄H₆N₂S. 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
Tapazole is indicated in the medical treatment of hyperthyroidism. Long-term therapy may lead to remission of the disease. Tapazole may be used to ameliorate hyperthyroidism in preparation for subtotal thyroidectomy or radioactive iodine therapy. Tapazole is also used when thyroidectomy is contraindicated or not advisable.

CONTRAINDICATIONS
Tapazole 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

Continued on next page

Tapazole—Cont.

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 Tapazole 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.

Tapazole can cause fetal harm when administered to a pregnant woman. Tapazole 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 Tapazole during pregnancy. If Tapazole 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 Tapazole in pregnant women requiring treatment with antithyroid drugs.

Postpartum patients receiving Tapazole should not nurse their babies.

PRECAUTIONS

General—Patients who receive Tapazole 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 Tapazole 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 thyroid function is warranted, and the finding of an elevated TSH warrants a decrease in the dosage of Tapazole.

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

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—Tapazole 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 Tapazole 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).

Usage in Children—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 hypoglycemia 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/mm³), often with relative granulocytopenia.

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, exfolia-

tive 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 overdose, 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

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

Adult—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

Tapazole® Tablets, are available in:
The 5-mg tablets (UC5385) are white in color, round, beveled, scored, and debossed with "J94".

They are available as follows:

Bottles of 100 NDC 52604-1094-1
(No. 1765)

The 10-mg tablets (UC5386) are white in color, round, beveled, scored, and debossed with "J95".

They are available as follows:

Bottles of 100 NDC 52604-1095-1
(No. 1770)

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

CAUTION—Federal (USA) law prohibits dispensing without prescription.

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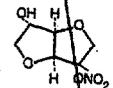
IMDUR®
(Isosorbide mononitrate)
Extended Release Tablets

DESCRIPTION

Isosorbide mononitrate (ISMN), an organic nitrate and a major biologically active metabolite of isosorbide dinitrate (ISDN), is a vasodilator with effects on both arteries and veins.

IMDUR Tablets contain 90 mg, 60 mg, or 120 mg of isosorbide mononitrate in an extended-release formulation. The inactive ingredients are aluminum silicate, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, paraffin wax, polyethylene glycol, titanium dioxide, and trace amounts of colorant.

The chemical name for ISMN is 1,4:3,6-dianhydro-2,3,4,5-tetrahydro-2H-pyrido[4,3-b]pyridin-5-nitrate; the compound has the following structural formula:



ISMN is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of about 90°C, and an optical rotation of +144° (2% in water, 20°C). Isosorbide mononitrate is freely soluble in water, ethanol, methanol, chloroform, ethyl acetate, and dichloromethane.

CLINICAL PHARMACOLOGY

Mechanism of Action The IMDUR® product is an extended-release formulation of ISMN, the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate is attributable to the mononitrate.

The principal pharmacological action of ISMN and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood, decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and systolic arterial pressure and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs.

The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Pharmacodynamics Dosing regimens for most chronic anginal used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only nitrates have been absent from the body for several hours after their antianginal efficacy has been restored. IMDUR Tablets during long-term use over 42 days dosed at 120 mg once daily continued to improve exercise performance at 12 hours and at 12 hours after dosing but its effects (although

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