

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

May 17, 2000

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OVERNIGHT COURIER

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Methimazole Tablets, USP, 15 mg and 20 mg are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Methimazole Tablets, USP, 15 mg and 20 mg are suitable for submission as ANDAs. The listed reference drug product upon which this petition is based is Tapazole® Tablets (methimazole), 5 mg and 10 mg manufactured by Eli Lilly and Company (distributed by Jones Pharma Incorporated). See listing on page 3-227 of the Twentieth Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Attachment 1). Therefore, the petitioner seeks a change in strength (from 5 mg and 10 mg to include a 15 mg and 20 mg strength) from that of the listed drug product.

B. Statement of Grounds

The reference listed drug (RLD) product is currently available in tablets consisting of either 5 mg or 10 mg of methimazole. The proposed drug product represents tablets that will contain higher strengths of the drug (15 mg and 20 mg). These additional strengths are believed to be consistent with the currently approved RLD product's labeling and will provide a more convenient single

00P-1308

CPI

dosage unit to provide the specific dose required by the individual patient and prescribed by the physician. The petition is thus seeking a change in strength (from 5 mg and 10 mg to include a 15 mg and 20 mg strength) from that of the reference listed drug.

The approved labeling of the RLD provides the following dosage and administration instructions for Methimazole:

Methimazole 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.

It is clear from the labeling of the approved drug product that dosage strengths of 15 mg and 20 mg are clearly contemplated as typical doses for the approved indications. In addition, it is clear that tablets in dosage strengths of 15 mg and 20 mg may be useful in providing either maintenance doses or doses titrated to an individual patient's needs that would allow the patient to take far fewer tablets to achieve the appropriate dose.

The petitioner is seeking the requested changes in strength from the RLD drug product to provide the physician greater flexibility in administering alternate dosage strengths that are consistent with doses contemplated in the labeling of the RLD. The goal being to reduce the number of tablets a patient would need to take for a single dose. This will improve patient convenience, compliance and make it easier to achieve the required dose for those patients that either have difficulty in swallowing multiple tablets or because of their illness makes multiple tablet administration difficult.

Copies of labeling of the reference listed drug product upon which this petition is based and proposed draft labeling for the proposed product are included in Attachments 2 and 3, respectively. The proposed labeling is the "same as" that of the RLD labeling with the exception of changes allowed because the manufacturer of the generic product differs from that of the innovator and in the How Supplied section which lists the additional proposed strengths. There are no changes in the indications or dosage and administration sections necessary, as the approved labeling of the RLD already contemplates the use of the proposed dosage strengths.

Therefore, the petitioner requests that the Commissioner find that a change in strength from 5 mg and 10 mg tablets to include 15 mg and 20 mg strength tablets for this product raises no questions of safety or effectiveness, and the Agency should then approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

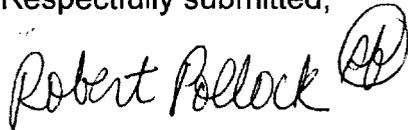
D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, 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.

Respectfully submitted,



Robert. W. Pollock
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

RWP/sf

Attachments: Prescription Drug Product List
Labeling of Tapazole[®], Methimazole Tablets, USP
Proposed Draft Labeling of Methimazole Tablets, USP

cc: Greg Davis (OGD)
Cecelia Parise (OGD)
Leon Lachman, Ph.D. (LCS)

Chp0138

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

PRESCRIPTION DRUG PRODUCT LIST

3-227

METHAZOLAMIDE

TABLET; ORAL

METHAZOLAMIDE

<u>AB</u>	APPLIED ANAL	<u>50MG</u>
<u>AB</u>	COPLEY PHARM	<u>25MG</u>
<u>AB</u>		<u>50MG</u>
<u>AB</u>	GENEVA PHARMS	<u>25MG</u>
<u>AB</u>		<u>50MG</u>
<u>AB</u>	INVAMED	<u>25MG</u>
<u>AB</u>		<u>50MG</u>
<u>AB</u>	MIKART	<u>25MG</u>
<u>AB</u>		<u>50MG</u>
<u>NEPTAZANE</u>		
<u>AB</u>	LEDERLE	<u>25MG</u>
<u>AB</u>	+	<u>50MG</u>

METHENAMINE HIPPURATE

TABLET; ORAL

HIPREX

<u>AB</u>	+ HOECHST MARION RSSL	<u>1GM</u>
<u>AB</u>	<u>UREX</u>	
	3M	<u>1GM</u>

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

<u>100MG/ML</u>	N86459 001
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ROBAXIN

AP + ROBINS AH

<u>100MG/ML</u>	N11790 001
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TABLET; ORAL

METHOCARBAMOL

AA CHELSEA LABS

500MG	N85180 001
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AA

750MG	N85192 001
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AA DANBURY PHARMA

500MG	N84277 001
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AA

750MG	N84276 002
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AA EON

500MG	N87283 001
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AA

750MG	N87282 001
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AA GENEVA PHARMS

500MG	N84616 001
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AA

750MG	N84615 001
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AA GLOBAL PHARM

500MG	N84927 001
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AA

750MG	N84928 001
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AA LANNETT

750MG	N84756 001
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AA LEDERLE

500MG	N85961 001
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AA

750MG	N85963 001
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AA NYLOS

750MG	N85033 001
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AA PAR PHARM

500MG	N86989 001
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AA

750MG	N86988 001
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AA SUPERPHARM

500MG	N87589 001
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AA

750MG	JAN 22, 1982
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AA

750MG	N87590 001
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AA TABLICAPS

500MG	JAN 22, 1982
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AA WEST WARD

500MG	N84846 001
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AA

750MG	N85159 001
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AA

750MG	N85123 001
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AA ROBAXIN

AA + ROBINS AH

500MG	N11011 004
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AA ROBAXIN-750

AA + ROBINS AH

750MG	N11011 006
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METHOCARBAMOL; *MULTIPLE*
SEE ASPIRIN; METHOCARBAMOL

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 2



PV 0372 UCP
TABLETS
TAPAZOLE®
METHIMAZOLE
TABLETS, USP

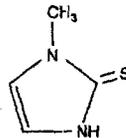
DESCRIPTION

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- instead of a 6-membered ring.

Each tablet contains 5 or 10 mg (43.8 or 87.6 μ mol) 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 $C_4H_6N_2S$. 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

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 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



DU 0372 UCP

Periodic monitoring of 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).

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

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, 15-30°C (59-86°F).



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LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

Proposed Draft Labeling

METHIMAZOLE TABLETS, USP

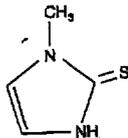
DESCRIPTION

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- instead of a 6-membered ring.

Each tablet contains 5, 10, 15 or 20 mg (43.8, 87.6, 131.4 or 175.2 μmol) methimazole, an orally administered antithyroid drug.

Each tablet also contains appropriate inactive ingredients.

The molecular weight is 114.16, and the empirical 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. Long-term 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.

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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, are available in:

The 5 mg tablets (code TBD) are XXX in color, round, scored and debossed with "Code TBD".

They are available as follows:

Bottles of 100 NDC XXXXX-XXXX-X

The 10 mg tablets (Code TBD) are XXX in color, round, scored and debossed with "Code TBD".

They are available as follows:

Bottles of 100 NDC XXXXX-XXXX-X

The 15 mg tablets (Code TBD) are XXX in color, round, scored and debossed with "Code TBD".

They are available as follows:

Bottles of 100 NDC XXXXX-XXXX-X

The 20 mg tablets (Code TBD) are XXX in color, round, scored and debossed with "Code TBD".

They are available as follows:

Bottles of 100 NDC XXXXX-XXXX-X

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

Manufactured by YYYYYY for ZZZZZZ

Label update 5/8/00