METHIMAZOLE TABLETS, USP

DESCRIPTION
Methimazole (4-methylthiouracil) is a white, crystalline substance that is freely soluble in water. It differs chemically from the drugs of the thiourea series primarily because it has a S, instead of a K mounted ring. Each tablet contains 3.5 or 15 mg of crystalline methimazole, an orally administered antithyroid drug. Each tablet also contains excipients: microcrystalline cellulose, magnesium stearate, colorants, and talc.

The molecular weight is 114.17, and the molecular formula is C₇H₉NOS. The structural formula is as follows:

CLINICAL PHARMACOLOGY

Methimazole inhibits the synthesis of thyroid hormones and is effective in the treatment of hyperthyroidism. The drug does not rapidly reduce existing thyroid hormone stores that are present in the thyroid gland or in the blood, nor does it interfere with the effectiveness of thyroid hormones given by or by injection. Methimazole is readily absorbed in the gastrointestinal tract, metabolized in the liver, and excreted in the urine.

INDICATIONS AND USAGE

Methimazole is indicated:

- For the treatment of hyperthyroidism in adults and children.
- For the prophylactic treatment of hyperthyroidism in patients who have undergone subtotal thyroidectomy or who are undergoing medical treatment before surgery.

CONTRAINDICATIONS

Methimazole is contraindicated in the presence of hypersensitivity to the drug or any of its other products components.

WARNINGS

Con genital Malformations

Methimazole readily crosses placental membranes and can cause fetal harm, particularly when administered in the first trimester of pregnancy. When methimazole is used during pregnancy, it is unknown if the drug causes harm to the fetus, the patient should be warned of the potential hazard to the fetus.

Liver Toxicity

Although there have been reports of hepatitis (including acute liver failure) associated with methimazole, the risk of hepatitis appears to be less with methimazole than with propylthiouracil, especially in the pediatric population. Symptoms suggestive of hepatic dysfunction (anorexia, jaundice, right upper quadrant pain, and tenderness) should prompt withdrawal of the drug. The patient should be followed closely if continued administration is contemplated.

Hypothyroidism

Methimazole can cause hypothyroidism necessitating routine monitoring of TSH and free T₄ levels with adjustment in dosage to maintain a euthyroid state. Because the drug readily crosses placental membranes, methimazole can cause hypothyroidism in the neonate. It is important to discontinue the drug before delivery if pregnanacy is suspected to prevent iatrogenic cretinism.

PRECAUTIONS

General

Patients who receive methimazole should be under close observation and should be rechecked to report immediately any evidence of illness, particularly acute oropharyngeal, fever, headache, or general malaise. In such cases, withdrawal and differential therapy should be obtained to determine whether hypothyroidism has developed. Particular care should be exercised with patients who are receiving additional drugs known to cause hypothyroidism.

Laboratory Tests

Because methimazole may cause hypothyroidism and bleeding, periodic tests should be monitored during therapy with the drug, especially before surgical procedures.

Thyroid function tests should be monitored periodically during therapy. Once clinical evidence of hypothyroidism has resolved, the finding of a low serum TSH indicates that a lower maintenance dose of methimazole should be employed.

Drug Interactions

Anticoagulants (oral) - Due to potential inhibition of vitamin K activity by methimazole, the anticoagulant effect may be increased; additional monitoring of PT/INR should be considered, especially before surgical procedures.

Estrogens, progestogens - Hyperthyroidism may cause an increased clearance of beta blockers with a higher intensity ratio. A reduced dose of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year rat studies were given methimazole at doses of 0.5, 3, and 15 mg/kg/day. These doses were 0.2, 1.2, and 10 times (on a mg/m² basis) the human daily maintenance dose when calculated on the basis of surface area. Thyroid hyperplasia, adenomas, and carcinomas developed in rats at two of the higher doses. The clinical significance of these findings is unknown.

Pregnancy Category D

Due to the rare occurrence of congenital malformations associated with methimazole use, it may be appropriate to use other agents in pregnant women requiring treatment for hyperthyroidism, particularly in the first trimester of pregnancy (organogenesis).

Patients should be advised that if they become pregnant or intend to become pregnant while taking an antithyroid drug, they should inform their physician immediately about their therapy.

In pregnant women, the thyroid dysfunction diminishes as the pregnancy progresses; consequently, a reduction in dosage of antithyroid drug may be possible. In some instances, antithyroid therapy can be discontinued 2-3 weeks before delivery. Because the drug may readily cross placental membranes, methimazole can cause fetal goiter and pretibial myxedema when administered to the mother in the third trimester. For this reason, it is important that a sufficient, but not excessive, amount of the drug be continued during pregnancy. (See WARNINGS.)

Nursing Mothers

Methimazole is excreted into breast milk. However, several studies found no effect on clinical status in nursing infants. In some instances, Methimazole may be administered to the mother in postpartum period. (See WARNINGS.)

Pediatric Use

Because of pharmacokinetic reports of severe liver injury in pediatric patients treated with propylthiouracil, methimazole is the preferred choice when an antithyroid drug is required in a pediatric patient. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Major adverse reactions (which occur with much greater frequency than the minor adverse reactions) include inhibition of thyroxine (L-thyroxine), triiodothyronine, and thyroxine and triiodothyronine (L-thyroxine, L-thyroxine). The symptoms may include: fatigue, weakness, malaise, weight gain, cold intolerance, constipation, diarrhea, edema, dry skin, hair loss, heat intolerance, muscle cramps, myalgia, myasthenia, nervousness, pallor, pain, pathological fracture, paresthesia, polyuria, pruritus, rash, reactivation of cutaneous lupus, Raynaud’s phenomenon, headache, fever, flu-like illness, nausea, vomiting, diarrhea, fever, joint pain, pruritus, and odema.

In addition to the above, seizures or coma have been reported in adults and children given methimazole at high dosages. These conditions have been reported to occur in methimazole-treated patients with hyperthyroidism before antithyroid therapy had been initiated. The onset of these conditions was usually acute and occurred within one week after the start of methimazole therapy.

In the past, severe cutaneous reactions of an allergic type, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported with methimazole therapy. These reactions may be associated with high serum concentrations of the drug.

OVERDOSAGE

Symptoms of overdose may include nausea, vomiting, salivation, diarrhea, pruritus, fever, joint pain, pruritus, and odema. Life-threatening symptoms or coma may occur with ingestion of a toxic dose. The serum level of methimazole in those patients who have become symptomatic is unknown. However, the symptoms noted in these patients generally resolved after discontinuation of the drug.

In severe toxicity, fatalities have occurred. In such cases, single doses of 0.4 mg/kg or more of orally administered methimazole have been reported. However, the frequency and extent of adverse reactions are unknown with drug-induced hepatitis, and unusual drug toxicities in the patient. In the event of an overdose, appropriate supportive therapy should be initiated as directed by the patient’s medical status.

DOSAGE AND ADMINISTRATION

Methimazole is administered orally. The total daily dosage is usually given in 3 divided doses at approximately 8-hour intervals.

Adults

The initial daily dosage is 15 mg to initiate treatment, 30 to 45 mg to moderate severe hyperthyroidism, and 60 mg to severe hyperthyroidism, divided into 3 doses at bedtime. The maintenance dosage is 3 to 15 mg/day.

Pediatric

The initial daily dosage is 0.4 mg/kg of body weight divided into 3 doses and given at bedtime. The maintenance dosage is approximately 1/2 of the initial dose.

HOW SUPPLIED

Methimazole Tablets, USP 5 mg - white to off-white, round, flat, scored, bevel-edge tablets, scored with 5 on one side and plain on the other.

They are available in:

- Bottles of 100
  - NDC 0466-846-01
  - NDC 0466-846-06

Methimazole Tablets, USP 10 mg - white to off-white, round, flat, scored, bevel-edge tablets, scored with 10 on one side and plain on the other.

They are available in:

- Bottles of 100
  - NDC 0466-841-01
  - NDC 0466-841-06

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

Dispense in tight, light-resistant containers.

Manufactured and Distributed by:
PAR PHARMACEUTICAL COMPANIES, INC.
Spring Valley, NY 10977

Revised: 01/10
OS649-01-11-10