CI 4974-4

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# PROPYLTHIOURACIL TABLETS, USP

CI 4974-4

Lederle

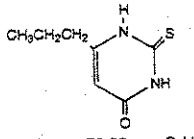
# PROPYLTHIOURACIL TABLETS, USP

℞ only

## DESCRIPTION

Propylthiouracil (6-propyl-2-thiouracil) is one of the thiocarbamide compounds. It is a white, crystalline substance that has a bitter taste and is very slightly soluble in water.

Propylthiouracil is an antithyroid drug administered orally. The structural formula is:




Molecular Weight: 170.23 $C_7H_{10}N_2OS$

Each tablet contains propylthiouracil 50 mg and the following inactive ingredients: corn starch, docusate sodium, magnesium stearate, microcrystalline cellulose, modified food starch, sodium benzoate, and sodium starch glycolate.

## CLINICAL PHARMACOLOGY

Propylthiouracil 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.

Propylthiouracil is readily absorbed from the gastrointestinal tract. It is metabolized rapidly and requires frequent administration. Approximately 35% of the drug is excreted in the urine, in intact and conjugated forms, within 24 hours.

In laboratory animals, various interventions, including propylthiouracil administration, that continuously suppress thyroid function and thereby increase TSH secretion result in thyroid tissue hypertrophy.

## INDICATIONS AND USAGE

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

**CONTRAINDICATIONS**

Propylthiouracil is contraindicated in the presence of hypersensitivity to the drug or any of the other product components and in nursing mothers because the drug is excreted in milk.

## WARNINGS

Agranulocytosis is potentially the most serious side effect of propylthiouracil therapy. Patients should be instructed to report 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), ANCA-positive vasculitis, hepatitis, interstitial pneumonitis, fever, or exfoliative dermatitis. The patient's bone marrow function should be monitored.

Propylthiouracil can cause fetal harm when administered to a pregnant woman. Because the drug readily crosses placental membranes and can induce goiter and even cretinism in the developing fetus, it is important that a sufficient, but not excessive, dose be given. In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently a reduction of dosage may be possible. In some instances, propylthiouracil can be withdrawn 2 or 3 weeks before delivery.

If this drug 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.

Postpartum patients receiving propylthiouracil should not nurse their babies.

Rare reports exist of severe hepatic reactions including encephalopathy, fulminant hepatic necrosis, and death in patients receiving propylthiouracil. Symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.) should prompt evaluation of liver function. Treatment with propylthiouracil should be discontinued promptly in the event of clinically significant evidence of liver abnormality, including hepatic transaminases in excess of 3 times the upper limit of normal.

## PRECAUTIONS

**General**

Patients who receive propylthiouracil should be under close surveillance and should be impressed with the necessity of reporting 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.

**Information for Patients**

Patients should be advised that if they become pregnant during therapy or intend to become pregnant, they should contact their physician immediately about the desirability of discontinuing the drug. They also should not use propylthiouracil while nursing.

Patients should report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. They also should report symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.).

**Laboratory Tests**

Because propylthiouracil may cause hypoprothrombinemia and bleeding, prothrombin time 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 hyperthyroidism has resolved, the finding of an elevated serum TSH indicates that a lower maintenance dose of propylthiouracil should be employed.

**Drug Interactions**

*Anticoagulants (oral):* The activity of anticoagulants may be potentiated by anti-vitamin-K activity attributed to propylthiouracil.

*β-adrenergic blocking agents:* Hyperthyroidism may cause an 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; a 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**
Laboratory animals treated with propylthiouracil for >1 year have demonstrated thyroid hyperplasia and carcinoma formation.[1] Such animal findings are seen with continuous suppression of thyroid function by sufficient doses of a variety of antithyroid agents, as well as in dietary iodine deficiency, subtotal thyroidectomy, and implantation of autonomous thyrotropic hormone-secreting pituitary tumors. Pituitary adenomas have also been described.

**Pregnancy**

*Pregnancy Category D.*
See **WARNINGS.**

**Nursing Mothers**
The drug appears in human milk and is contraindicated in nursing mothers. See **CONTRAINDICATIONS** and **WARNINGS.**

**Pediatric Use**
Safety and effectiveness in pediatric patients below the age of 6 have not been established. For pediatric patients 6 years of age and older, see **DOSAGE AND ADMINISTRATION.**

## ADVERSE REACTIONS

Major adverse reactions (much less common than the minor adverse reactions) include inhibition of myelopoiesis (agranulocytosis, granulopenia, and thrombocytopenia), aplastic anemia, drug fever, a lupus-like syndrome (including splenomegaly and vasculitis), hepatitis, periarteritis, and hypoprothrombinemia and bleeding. Nephritis, glomerulonephritis, interstitial pneumonitis, exfoliative dermatitis, and erythema nodosum have been reported. Reports of a vasculitic syndrome associated with the presence of anti-neutrophilic cytoplasmic antibodies (ANCA) have also been received. Manifestations of ANCA-positive vasculitis may include rapidly progressive glomerulonephritis (crescentic and pauci-immune necrotizing glomerulonephritis), sometimes leading to acute renal failure; fever; pulmonary infiltrates or alveolar hemorrhage; skin ulcers; and leucocytoclastic vasculitis.

Minor adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesias, loss of taste, taste perversion, 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**

Nausea, vomiting, epigastric distress, headache, fever, arthralgia, pruritus, edema, and pancytopenia. Agranulocytosis is the most serious effect. Rarely, exfoliative dermatitis, hepatitis, neuropathies, or CNS stimulation or depression may occur.

No information is available on the following: $LD_{50}$; concentration of propylthiouracil in biologic fluids associated with toxicity and/or death; the amount of drug in a single dose usually associated with symptoms of overdosage; or the amount of propylthiouracil in a single dose likely to be life-threatening.

**Treatment**

To obtain up-to-date information about the treatment of overdose, a good resource is the 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 the 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 propylthiouracil.

## DOSAGE AND ADMINISTRATION

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

**Adults**

The initial dose is 300 mg daily. In patients with severe hyperthyroidism, very large goiters, or both, the beginning dosage usually should be 400 mg daily; an occasional patient will require 600 to 900 mg/day initially. The usual maintenance dosage is 100 to 150 mg daily.

**Pediatric Patients**

For pediatric patients 6 to 10 years of age, the initial dosage is 50 to 150 mg daily. For pediatric patients 10 years and over, the initial dosage is 150 to 300 mg daily. The maintenance dosage is determined by the response of the patient.

## HOW SUPPLIED

Propylthiouracil Tablets, USP, 50 mg, are round, white, scored tablets, engraved LL and P33, supplied as:

NDC 0005-4609-23 - Bottle of 100
NDC 0005-4609-34 - Bottle of 1000

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

REFERENCE

1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. 1974; 7; 67-76.

STANDARD PRODUCTS

LEDERLE PHARMACEUTICAL DIVISION
of American Cyanamid Company
Pearl River, NY 10965

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