PTU™ 50 mg Tablets

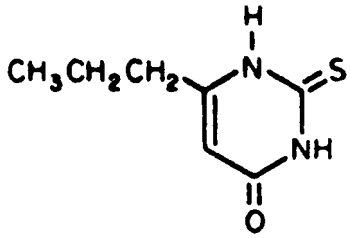
NAME OF THE MEDICINE

Propylthiouracil

Chemical Name: 1,2-dihydro-6-propyl-2-thioxopyrimidine-4-one

The molecular weight of the compound is 170.2, the molecular formula is $C_7H_{10}N_2OS$ and the CAS registry number is *51-52-5.*

Structural Formula:



DESCRIPTION

Propythiouracil is a thioamide derivative which occurs as a white crystalline powder, odourless with a bitter taste, very slightly soluble in water, sparingly soluble in ethanol and soluble in solutions of alkali hydroxides or ammonia.

PTU™ 50 mg Tablets are white, round, biconvex and uncoated. One side is debossed 'PRESTAB' and other side is plain.

PHARMACOLOGY

Category: Antithyroid

Propylthiouracil blocks the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) by inhibiting incorporation of iodide into tyrosine.

Propylthiouracil is rapidly absorbed. The half-life in plasma approximates 2 hours (in anuric patients T½ 8.5 hours). Protein binding of propylthiouracil is approximately 75%. The drug is metabolized in the liver and is excreted in the bile (primary route) with approximately 30% being excreted in the urine as metabolites or whole drug. Propylthiouracil does not interfere with the action and the release of exogenous thyroid hormone. Clinical response, therefore, does not occur until circulating and colloid-stored thyroid hormone is utilised, and as such depends in part on the amount of colloid in the gland. The rapid fall in serum triiodothyronine T_3 concentration, before serum thyroxine (T_4) levels fall, parallels a clinical improvement in the thyrotoxic patient, and is generally seen after the first week. The patient may become euthyroid after 4-6 weeks.

Propylthiouracil does not interfere with the effectiveness of thyroid hormones given by mouth or injection. Prolonged administration of propylthiouracil may result in hyperplasia of the thyroid gland due to pituitary thyrotrophic hyperactivity induced by diminished thyroxine secretion.

INDICATIONS

Propylthiouracil is an antithyroid drug indicated for the total treatment of hyperthyroidism or in the treatment of the thyrotoxic patient prior to surgery or radioactive-iodine therapy.

CONTRAINDICATIONS

Patients who are known to be hypersensitive to propylthiouracil or related thioamide derivatives.

PRECAUTIONS

In preparing patients for surgery, the administration of iodine is recommended concomitantly with propylthiouracil to decrease the vascularity and friability of the thyroid gland.

Although propylthiouracil is used for the total treatment of hyperthyroidism, duration of treatment necessary to produce a prolonged remission varies from 6 months to several years, with an average duration of one year. Remission has occurred in at least 50% of patient's 6-12 months after cessation of medication.

In view of the fact that hypothyroid patients seem to have poor adrenergic nervous function, use with caution in patients with asthma.

Patients should be closely supervised during prolonged propylthiouracil therapy because of the likelihood of agranulocytosis. Patients should be warned to report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, chills, headache, and malaise. All patients receiving propylthiouracil should have regular full blood counts as well as close monitoring of liver and thyroid function tests (See "**Interaction with Other Medicines**" and "**Adverse Effects**").

Regular thyroid function tests are recommended in patient monitoring (recommended prior to initiation of therapy, at monthly intervals during stabilization, then every 2 to 3 months) viz Free (unbound) Serum Thyroxine (T_4) levels, Total Serum T_4 levels, Serum Thyrotropin (TSH), Total Serum Triiodothyronine (T_3). Liver Function Tests are also recommended at periodic intervals during therapy.

Use in Pregnancy
Propylthiouracil is pregnancy category C

Propylthiouracil freely crosses the placenta, and the safety of this product for use during pregnancy has not been fully established. Propylthiouracil may damage the foetal thyroid and produce foetal hypothyroidism and neonatal goitre, or cause congenital abnormalities in the neonate (vide infra).

In administering propylthiouracil during pregnancy, careful consideration should be given to the dosage for individual patients to provide the required therapeutic effect compatible with minimum risk to the foetus from potential toxicity. The dose should be set as low as possible since there is evidence that neonatal goitre is less likely if the mother receives less than 100 mg of propylthiouracil per day. After control of thyrotoxicosis, the dose of propylthiouracil should be gradually decreased to 50 mg twice daily. If there is the slightest suspicion of hypothyroidism in the pregnant patient, the drug should be temporarily discontinued and thyroid hormone given.

Three cases of scalp defects in the offspring of mothers, and two siblings with aplasia cutis in one mother, who were on methimazole, a related thioamide derivative, have been reported.

Use in Lactation
Propylthiouracil is excreted in breast milk. Breast feeding should be terminated prior to initiation of therapy.

Interactions with Other Medicines
Because propylthiouracil can cause hypoprothrombinanaemia, extreme caution is advised in patients receiving oral anticoagulants or heparin. Prothrombin times should be carefully monitored during therapy.

Agranulocytosis Producing Medications
Concurrent use may increase the risk of agranulocytosis.

Effect on Laboratory Tests
Prothrombin Time, Serum alkaline phosphatase, Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic-pyruric transaminase (SGPT) levels may be increased.

ADVERSE EFFECTS

Note: Incidence of adverse effects is directly related to dosage.

The overall incidence of side effects with propylthiouracil is of the order of 3%.

Incidence less frequent: Inhibition of haemopoiesis (agranulocytosis, granulocytopenia, leucopenia, thrombocytopenia) is the most serous side effect. The incidence of agranulocytosis approaches 0.5%. Agranulocytosis usually occurs during the first two months of therapy and then the incidence gradually declines. Mild leucopenias occur more frequently, and approximately 10% of untreated hyperthyroid patients have leucocyte levels below 4.0 x 10^9/L. It should be noted that about 10% of patients with untreated hyperthyroidism have leucopenia (white blood cell count 4000/cu mm), often with relative granulocytopenia.

Incidence rare:

- Yellowing of eyes and skin (cholestatic jaundice)
- Loss of hearing (ototoxicity)
- Swollen lymph nodes (lymphadenopathy)
- Unusual bleeding or bruising (hypoprothrombinemia, factor VII or proconvertin deficiency, thrombocytopaenia)
- Unusual increase or decrease in urination, backache, swelling of feet or lower legs (nephritis)

Signs of overdosage or hypothyroidism: Changes in menstrual periods, coldness, constipation, dry, puffy skin, headache, listlessness, muscle aches, sleepiness, tiredness, unusual weight gain, weakness.

Signs of thyrotoxicosis or inadequate therapy: Diarrhoea, fever, irritability, listlessness, rapid or irregular heartbeat, vomiting, weakness.

Those indicating need for medical attention only if they continue or are bothersome.

Incidence more frequent: Itching

Incidence less frequent: Dizziness, joint pain, loss of taste, nausea and vomiting (possible overdose), numbness or tingling of fingers, toes, or face (peripheral neuropathy, possible overdose), skin rash (hypersensitivity).

Note: may disappear spontaneously with continued treatment; appears to be dose-related. Stomach pain.

Incidence rare: Darkening of skin, lightening of hair colour, loss of hair, sore, red, watery eyes (recurrent keratitis, conjunctival disorders).

Hepatotoxicity: Propylthiouracil-related hepatotoxicity is a major but rare side effect. The frequency ranges from 0.1 percent to 0.2 percent and takes the form of an allergic hepatitis accompanied by laboratory evidence of heptacellular injury. This includes markedly elevated amino-transferase levels and submassive or massive hepatic necrosis on biopsy. The danger of permanent hepatic damage should be kept in mind. The best way of preventing propylthiouracil hepatotoxicity is careful screening of patients considered for treatment.

Women less than 30 years of age have a higher incidence of propylthiouracil induced hepatotoxicity and the average duration of propylthiouracil therapy before the onset of hepatotoxicity is approximately three months. Monitoring hepatic enzymes on a monthly basis for the first six months of treatment has been suggested. Patients on propylthiouracil treatment should be counselled to report signs and symptoms of hepatotoxicity, such as upper abdominal discomfort, fever, nausea and vomiting together with weight-loss.

Vasculitis: Vasculitis is a rare complication of propylthiouracil therapy. Serological evidence consistent with lupus erythematosus develops in some patients, fulfilling the criteria for drug-induced lupus. There are 32 cases of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis in association with anti-thyroid medication reported in the English literature. Approximately 90% of cases related to propylthiouracil. The clinical features of anti-thyroid drug induced ANCA-positive asculitis include renal involvement (67%), arthralgia (48%), fever (37%), skin involvement (30%), respiratory tract involvement (27%) and other manifestations (18%).

DOSAGE AND ADMINISTRATION

Propylthiouracil is administered orally, usually in 2 to 4 equal doses at 12 to 6 hourly intervals respectively.

Dosage in Adults
The usual initial controlling dose of propylthiouracil is 200-400 mg daily (range 100-1200 mg) in divided doses (three doses at eight-hour intervals or four doses at six-hour intervals) until the patient becomes euthyroid.

NB: Patients with severe hyperthyroidism may require up to 1,200 mg a day.

Maintenance Dose:	50-800 mg daily in two to four divided doses.
Thyrotoxic Crisis:	Concomitant with the administration of other agents, e.g. iodine, adrenergic blocking agents, and general supportive measures, the recommended dose of propylthiouracil is 800-1200 daily in divided doses administered orally or by naso-gastric tube.

Dosage in Children

Initial:	Calculated on 50 mg/m^2 of body surface three times a day.
6-10 years:	50 to 300 mg a day in two or three divided doses.
10 years and over:	150 to 600 mg a day divided into three doses at eight-hour intervals.
Maintenance Dose:	50-100 mg daily as determined by response.

Neonatal thyrotoxicosis: 10 mg per kg of body weight a day in divided doses.

OVERDOSAGE

Agranulocytosis is the most serious adverse effect resulting from overdose and/or prolonged administration.
Hypothyroidism may result from prolonged therapy (See "***Adverse Effects***").

General management of overdosage may consist of gastric lavage, observation, and symptomatic and supportive therapy.

Treatment is directed at the specific adverse effect e.g. in bone marrow depression, treatment by way of blood transfusion of fresh whole blood, antibiotics, and corticosteroids are used. Prothrombin deficiency associated with a haemorrhagic diathesis may be counteracted by phytomenadione.

In Australia, contact the Poisons Information Centre on 13 11 26 for further advice on overdose management.

PRESENTATION

PTU™50mg Tablets contain 50 mg of the active ingredient propylthiouracil. The inactive ingredients are lactose, magnesium stearate, povidone, sodium lauryl sulphate and maize starch. PTU™ 50mg Tablets are supplied in bottles containing 100 tablets. Store below 30°C.

Phebra Product Code: TAB001

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POISONS SCHEDULE

ScheduleS4 – Prescription Only Medicine.

SPONSOR

Phebra Pty Ltd, 332 Burns Bay Road, Lane Cove NSW 2066, Australia.
Telephone: 1800 720 020

Date of TGA Approval: August 1996
Safety Related Notification: 24th January 2007
Date of last amendment: 18th May 2010

Version 07