PTU™ 50 MG TABLETS
(PROPYLTHIOURACIL)

1 NAME OF THE MEDICINE

Propylthiouracil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Propylthiouracil 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 contain 50 mg of the active ingredient propylthiouracil.

Excipients with known effect: lactose monohydrate. The tablet is gluten free.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 mg daily in divided doses administered orally or by naso-gastric tube.

Dosage in children

Propylthiouracil use should be avoided in children, except in rare circumstances in which alternative therapies are not appropriate options. In circumstances where PTU™ is used, careful titration with the advice of a specialist is recommended.

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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 patients 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 **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions** and **Section 4.8 Adverse Effects (Undesirable 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.

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 hepatocellular 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.

Hepatotoxicity resulting in liver failure, liver transplantation, or death, has been reported with propylthiouracil therapy in adults and children.

Agranulocytosis producing medications

Concurrent use may increase the risk of agranulocytosis.

Use in the elderly

No data available.

Paediatric use

Propylthiouracil is not recommended for use in children except where carbimazole is not well-tolerated and surgery or radioactive iodine therapy are not appropriate therapies.

Effects on laboratory tests

Prothrombin Time, Serum Alkaline Phosphatase, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) levels may be increased.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Propylthiouracil is Pregnancy Category D - Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

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).

Propylthiouracil is suggested for use prior to conception and in the first trimester of pregnancy where clinically appropriate due to the higher risk of congenital abnormalities with carbimazole during fetal organogenesis in the first trimester.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 more frequent: Itching.

Incidence less frequent
Inhibition of haemopoiesis (agranulocytosis, granulocytopenia, leucopenia, thrombocytopenia) is the most serious 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 4,000/mm^3), often with relative granulocytopenia.

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
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). There have also been reports of serious hypersensitivity reactions (e.g. Stevens Johnson syndrome and toxic epidermal necrolysis). Other adverse reactions include urticaria, epigastric distress and paraesthesia.

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

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.

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 hepatocellular 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.

Severe adverse reactions include liver injury presenting as hepatitis, liver failure necessitating liver transplant or resulting in death. Nephritis, glomerulonephritis, interstitial pneumonitis, exfoliative dermatitis and erythema nodosum have also been reported.

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 vasculitis include renal involvement (67%), arthralgia (48%), fever (37%), skin involvement (30%), respiratory tract involvement (27%) and other manifestations (18%).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Agranulocytosis is the most serious adverse effect resulting from overdose and/or prolonged administration. Hypothyroidism may result from prolonged therapy (see **Section 4.8 Adverse Effects (Undesirable 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Category: Antithyroid.

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

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Propylthiouracil is rapidly absorbed.

Distribution

Protein binding of propylthiouracil is approximately 75%.

Metabolism

The drug is metabolized in the liver.

Excretion

The half-life in plasma approximates 2 hours (in anuric patients $T_{½}$ 8.5 hours).

The drug is excreted in the bile (primary route) with approximately 30% being excreted in the urine as metabolites or whole drug.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and maize starch.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

PTU™ 50 mg Tablets are supplied in bottles containing 100 tablets.

Phebra Product Code - TAB001.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

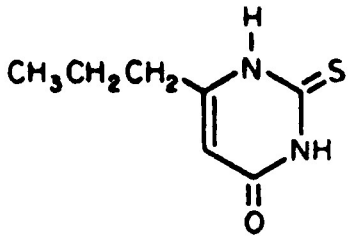
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

The molecular weight of the compound is 170.2, the molecular formula is $C_7H_{10}N_2OS$.

Chemical structure



CAS number

51-52-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

[1] AUST R 13319

8 SPONSOR

Phebra[2] Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
Ph: 1800 720 020

9 DATE OF FIRST APPROVAL

28 Aug 1991

10 DATE OF REVISION

04 Aug 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Safety related request to update the pregnancy category of PTU

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