

PRESCRIBING INFORMATION

^{Pr}**PROPYL-THYRACIL**[®]

(propylthiouracil tablets USP)

Thyroid Inhibitor

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Thyroid Inhibitor

ACTION

Propylthiouracil affects the synthesis of thyroid hormones by inhibiting the incorporation of iodide into thyroglobulin. It does not inactivate thyroid hormones previously formed or interfere with their release from the gland.

Also, depending on the activity of the disease and on whether or not the patient has previously received iodide, the clinical effects will not appear until the stored supply of thyroid hormones has been utilized.

Clinical response may be delayed for up to two weeks. Propylthiouracil may also decrease the rate of conversion of T₄(1-thyroxine) to T₃(triiodothyronine) in peripheral tissues.

Iodide uptake is not decreased by propylthiouracil.

In responsive patients, prolonged remission may be obtained only after several months of treatment and may take up to several years. The average duration of treatment is usually one year.

Data suggest that stopping therapy as soon as the euthyroid state is attained is as effective in some patients as continuing therapy for a year or longer.

INDICATIONS

Propylthiouracil is indicated:

1. For the medical management of hyperthyroidism.
2. In conjunction with radioiodine to hasten recovery while awaiting the effects of radiation.
3. For control of thyrotoxicosis prior to surgery.
4. In the management of a thyroid storm in addition to other therapeutic measures.

CONTRAINDICATIONS

Hypersensitivity or idiosyncratic reaction to propylthiouracil.

Nursing mothers.

WARNINGS

Serious Warnings and Precautions

Liver toxicity (see Hepatic Function section below)

Hepatic Function: Liver injury resulting in liver failure, liver transplantation, or death, has been reported with propylthiouracil therapy in adult and pediatric patients. No cases of liver failure have been reported with the use of methimazole in pediatric patients. For this reason, propylthiouracil is not recommended for pediatric patients except when methimazole is not well-tolerated and surgery or radioactive iodine therapy are not appropriate therapies. Propylthiouracil-induced hepatotoxicity is not dose-related and is thought to be idiosyncratic with an autoimmune component. Hepatocellular necrosis and fulminant hepatic failure have been reported in patients treated with propylthiouracil. Typically these reactions occur within the first two months of propylthiouracil treatment. Injury is reversible upon discontinuation of propylthiouracil although encephalopathy and/or substantial hepatic necrosis have been reported. Routine monitoring of serum transaminases is not required but may be recommended for patients with a history of liver disease or for those who have other risk factors for hepatitis, e.g., alcohol use. Discontinue propylthiouracil when signs and symptoms of hepatic injury are present. Further thionamide therapy is contraindicated as death has resulted upon rechallenge.

Vascular: Cases of vasculitis resulting in severe complications and death have been reported rarely in patients receiving propylthiouracil therapy. The cases of vasculitis include: glomerulonephritis, leukocytoclastic cutaneous vasculitis, alveolar/pulmonary hemorrhage,

cerebral angiitis, and ischemic colitis. Most cases were associated with anti-neutrophilic cytoplasmic antibodies (ANCA)-positive vasculitis. Early recognition of vasculitis is important to prevent long term organ damage and/or death. If vasculitis is suspected, discontinue propylthiouracil therapy and initiate appropriate intervention.

Use in Pregnancy: Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and fetal complications.

Propylthiouracil, used judiciously, is an effective drug for the treatment of hyperthyroidism in pregnant women. However, the drug readily crosses the placental barrier where it can induce goiter and hypothyroidism in the developing fetus. Rare cases of congenital anomalies have been observed post-marketing (See **Post-Market Adverse Reactions**). Epidemiological studies provide conflicting results regarding the risk of congenital anomalies.

Individual benefit/risk assessment is necessary before treatment with propylthiouracil during pregnancy. Propylthiouracil should be administered during pregnancy at the lowest effective dose, without additional administration of thyroid hormones. If propylthiouracil 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. Close maternal, fetal and neonatal monitoring of thyroid function is recommended, with adjustment of propylthiouracil as necessary.

Women of childbearing potential should use effective methods of contraception during Propyl-Thyracil therapy.

PRECAUTIONS

The dose of PROPYL-THYRACIL[®] should be reduced or temporarily discontinued if signs of hypothyroidism occur during treatment.

Blood formula should be determined prior to institution of treatment. Patients receiving propylthiouracil should be advised to notify their physician if fever, sore throat, unusual bleeding or bruising, or skin rash occurs. In such cases, white blood cell and differential counts should be made to determine whether severe leukopenia or agranulocytosis has developed.

Propylthiouracil has occasionally been reported to cause hypoprothrombinemia which would increase the effect of anticoagulants. Doses of oral anticoagulants, administered concurrently, should be adjusted accordingly.

The vascularity and size of the thyroid gland may increase during treatment with propylthiouracil. This suggests over treatment and indicates the need for reduced dosage.

When propylthiouracil is administered pre-operatively, iodine, in the form of a strong iodine solution (Lugol's solution or potassium iodide solution) should be given concomitantly for 7-10 days prior to surgery. The rationale for this is to reduce the vascularity and fragility of the thyroid gland.

Inform patients to promptly report symptoms that may be associated with vasculitis including new rash, hematuria or decreased urine output, dyspnea or hemoptysis.

ADVERSE REACTIONS

The more serious adverse reactions associated with propylthiouracil are agranulocytosis, hepatotoxicity and rarely, systemic vasculitis. Recovery is often possible following immediate cessation of the drug.

Blood

The incidence of agranulocytosis is less than 0.5%. It usually develops in the first few months of therapy, is dose-related and is reversible on rapid withdrawal of the drug.

Leukopenia with granulocytopenia, hemolytic anemia, thrombocytopenia, hypoprothrombinemia with hemorrhagic manifestations, aplastic anemia, myeloblastic leukemia and hyperglobulinemia have been reported.

Hepatic

Hepatotoxicity has an estimated frequency of 0.1-0.2% in patients treated with propylthiouracil. Propylthiouracil-induced hepatotoxicity is not dose-related and is thought to be idiosyncratic with an autoimmune component. Hepatocellular necrosis and fulminant hepatic failure have been reported in patients treated with propylthiouracil. Typically these reactions occur within the first two months of propylthiouracil treatment. Injury is reversible upon discontinuation of propylthiouracil although encephalopathy and/or substantial hepatic necrosis have been reported. (see **WARNINGS** section)

Skin

Urticaria, pruritus and a mild papular rash which may be accompanied by purpura are the most common skin reactions; (incidence approximately 3%).

Loss or depigmentation of the hair are less frequent.

Two cases of vesicular eruption in the newborn have been reported, secondary to maternal propylthiouracil therapy.

Miscellaneous

Nausea, vomiting, abdominal discomfort, drowsiness, headache, dizziness, arthralgia and paresthesia occur occasionally.

Very rare reactions

Drug fever, lymphadenopathy, splenomegaly, hepatitis, cholestatic jaundice, neuritis, nephritis, sialadenopathy, recurrent keratitis, conjunctival disorders, connective tissue disorders resembling polyarteritis, arthritis, lupus erythematosus and an ototoxic reaction presenting as unilateral sensorineural hearing impairment.

Post-Market Adverse Reactions

Cases of congenital anomalies have been rarely reported in neonates whose mothers were treated with propylthiouracil and other drugs during pregnancy. The pattern of congenital anomalies associated with propylthiouracil is unclear, but may include anal atresia, accessory auricle, intestinal malrotation, gastrointestinal malformation and ventricular septal defect (see WARNINGS section).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There has been one reported case of overdose with propylthiouracil in the literature where the patient developed Henoch-Schonlein purpura (HSP) for which causal relationship with the drug could not be confirmed.

Overdosage can result in enlargement of the thyroid gland, with signs and symptoms of hypothyroidism. This can be readily reversed by reducing or even temporarily withdrawing medication. Thyroxine replacement therapy, until the patient becomes euthyroid, may be indicated.

Overdosage in pregnant women may result in congenital goiter and hypothyroidism in the fetus. The newborn child should be examined carefully for signs of hypothyroidism and immediate thyroid therapy should be instituted if hypothyroidism is confirmed.

Haemorrhage may be controlled by the administration of vitamin K₁ and the dosage of PROPYL-THYRACIL[®] should be reduced.

DOSAGE AND ADMINISTRATION

Treatment with PROPYL-THYRACIL[®] should be individualized, according to the severity of symptoms and signs of hyperthyroidism and response to therapy.

Adults

The recommended initial dose is 50-100 mg (one to two PROPYL-THYRACIL[®] 50 mg tablets) every 8 hours, with increases as necessary up to a maximum of 500 mg/day. In some cases, initial doses as high as 900 mg/day may be required.

When doses larger than 300 mg/day of PROPYL-THYRACIL[®] are needed, the drug should be administered every 4 to 6 hours.

Usually after one or 2 weeks, but certainly after 3 weeks of therapy, objective signs of clinical improvement should be seen.

Delayed responses are sometimes noted when the thyroid is unusually large and when iodine in any form has previously been given.

The patient should be examined regularly by the physician and the dose of PROPYL-THYRACIL[®] adjusted until the patient is euthyroid (usually after 6-8 weeks). At this stage, the dose should be reduced by 1/3 every 4-6 weeks to a maintenance dosage of one tablet of PROPYL-THYRACIL[®] 50 mg two or three times daily, administered at regular intervals.

The course of therapy may last from 6 months to 3 years. Usually within one to two years, a prolonged remission in 50% of the cases can be expected.

When remission is observed, PROPYL-THYRACIL[®] should be withdrawn over a period of 1-2 months under close supervision.

Children

Initial dose guideline: 150 mg/m²/24 h

- for children 10 years of age and older: 150-300 mg/day in divided doses, at regular intervals.
- for children 6-10 years of age: 50-150 mg/day in divided doses, at regular intervals.

General maintenance dose: 50 mg b.i.d. when euthyroid.

In Renal Failure:

The following schedule is recommended by W.M. Bennett et al.:

Glomerular Filtration Rate (creatinine clearance)	10-50 mL/min	<10 mL/min
Reduce dose by	25% of the usual maintenance dose	50% of the usual maintenance dose

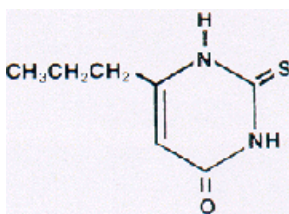
AVAILABILITY

Each white, round, biconvex tablet engraved with “PLB” on one side and “PPT” over score “50” on the other side, contains: propylthiouracil 50 mg. Available in bottles of 100 tablets.

Each white, round, biconvex tablet engraved with “PLB” on one side and “PPT” over score “100” on the other side contains: propylthiouracil 100 mg. Available in bottles of 100 tablets.

PHARMACOLOGY

Structural Formula:



Molecular Formula:



Chemical Name: 4(1H)-Pyrimidinone,2,3-dihydro-6-propyl-2-thioxo-6-Propyl-2-thiouracil

Molecular Weight: 170.23

Description: Propylthiouracil is a white, powdery, crystalline substance, starch-like in appearance and to the touch and having a bitter taste.

Solubility: It is slightly soluble in water, sparingly soluble in alcohol; slightly soluble in chloroform and in ether, soluble in ammonia and in alkali hydroxides.

It melts at about 219-221°C.

A saturated aqueous solution is neutral or slightly acid to litmus.

PROPYL-THYRACIL[®] is sensitive to light and must be stored in light-resistant containers.

Pharmacological Properties

Absorption of effective amounts occurs within 20 to 30 minutes after oral administration.

Propylthiouracil labelled with ³⁵S has been found to accumulate in the thyroid gland. Protein binding is about 40%.

It crosses the placental barrier and is found in the milk of nursing mothers.

The metabolites of propylthiouracil have not yet been satisfactorily identified. Propylthiouracil, to the extent of 50% of the dose, is conjugated to glucuronic acid and is mainly excreted via the kidneys within 24 hours. Only a small amount (1-3%) of the drug is found free in the urine.

The serum or plasma half-life ranges between 1-1.6 hours after a single oral dose.

The effect of a dose of 100 mg of propylthiouracil begins to wear off in 2 to 3 hours; a dose of 500 mg completely inhibits thyroid function for 6 to 8 hours.

Propylthiouracil inhibits the formation of thyroid hormones largely by interfering with the incorporation of iodine, into an organic form. This is probably done by interfering with the mechanism of oxidation of the iodide ion through thyroid peroxidase activities.

The observation that ¹³¹I iodine uptake remains elevated in hyperthyroid patients even when the euthyroid state is approached suggests that its action may be more complex, involving effects on organic binding and coupling.

The rapidity of the therapeutic response will depend largely on the completeness of blockade of thyroid hormones synthesis, the amount of stored hormones and the peripheral rate of turnover of these hormones.

The clinical response to propylthiouracil may be delayed for up to 2 weeks since the release of stored thyroid hormones is not affected.

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