

# **PROPYLTHIOURACIL TABLETS BP**

## **1 NAME OF THE MEDICINAL PRODUCT**

Propylthiouracil Tablets BP 50mg

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Propylthiouracil BP 50 mg

## **3 PHARMACEUTICAL FORM**

White biconvex uncoated tablets engraved Evans 184 on one face and plain on the other.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

1. Management of hyperthyroidism, including the treatment of Graves' disease and thyrotoxicosis.
2. Preparation of the hyperthyroid patient prior to surgery
3. An adjunct to radioactive iodine therapy.

### **4.2. Posology and method of administration**

Propylthiouracil is administered by the oral route.

Management of Hyperthyroidism

#### Adults

The initial dose of propylthiouracil is between 300mg and 600mg given as a single daily dose. This dose should be maintained until the patient is euthyroid. The dose should then be reduced gradually to a maintenance dose of between 50mg and 150mg, taken as a single daily dose.

Daily doses can be divided if preferred.

#### Children:

Children aged 6 - 10 years: Initial dose of 50-150mg daily

Children over 10 years: Initial dose of 150-300mg (or 150mg/m<sup>2</sup>) daily

Maintenance dose is determined by the patient's response.

#### Preparation for Surgery

As for management of hyperthyroidism, until the patient becomes euthyroid.

#### Adjunct to Radioactive Iodine Therapy

As for management of hyperthyroidism, for several weeks prior to radio-iodine treatment. Withdraw propylthiouracil 2 to 4 days before irradiation. The dosage of radio-iodine may need to be adjusted because propylthiouracil may have a radioprotective effect.

#### Management of Thyrotoxic Crisis

200mg every 4 to 6 hours for the first 24 hours, decrease the dose as the crisis subsides.

### Elderly

The adult dose should apply, but caution is advised in the presence of renal or hepatic impairment, where a dosage reduction may be justified.

### Renal impairment

Decrease the dose of propylthiouracil in renal failure. If the glomerular filtration rate is 10-50ml/min, decrease dose by 25%. If the GFR is <10ml/min decrease dose by 50%.

## **43                      Contraindications**

A known hypersensitivity to propylthiouracil and thioamide derivatives

## **4.4                      Special warnings and precautions for use**

All patients receiving propylthiouracil should have regular full blood counts.

Patients should be made aware that the development of certain adverse effects (fever, mouth ulcers, rashes, sore throat) may be an indication of agranulocytosis, a serious reaction to the drug, and they should contact their doctor immediately as treatment should be stopped. A full blood count should be performed if there is clinical evidence of infection. Likewise propylthiouracil should be used with extreme caution in patients receiving other drugs known to cause agranulocytosis. Use propylthiouracil with caution in patients more than 40 years old.

Propylthiouracil may cause hypothyroidism and bleeding so prothrombin time should be monitored during therapy, especially prior to surgery.

The thyroid function of patients receiving Propylthiouracil should be monitored regularly, viz free (unbound) serum thyroxine (T4) levels, total serum T4 levels, serum thyrotropin (TSH) and total serum triiodothyronine (T3). Thyroid function tests are recommended prior to initiation of therapy, at monthly intervals during stabilization, then every 2 to 3 months. Cross-sensitivity between antithyroid agents may occur

Prolonged therapy and/or excessive doses of propylthiouracil may cause hypothyroidism so thyroid function should be monitored regularly.

Another serious side effect is systemic vasculitis which can occur anytime and up to several years after initiation of treatment with propylthiouracil. Risk of systemic vasculitis may increase with prolonged use. Renal involvement is most common but skin, lung and musculoskeletal systems may also be involved. In severe cases death can occur. Propylthiouracil should be discontinued promptly and treatment initiated as required.

Some cases of severe hepatic reactions, both in adults and children, including fatal cases and cases requiring a liver transplant have been reported with propylthiouracil. Time to onset has varied but in a majority of cases the liver reaction occurred within 6 months. If significant hepatic enzyme abnormalities develop during treatment with propylthiouracil the drug should be discontinued immediately (see 4.8).

Propylthiouracil should not be used in paediatric patients unless the patient is allergic to or intolerant of the alternatives available

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The response of the thyroid gland to propylthiouracil may be impaired by a concurrent high iodine intake. Drug induced changes in thyroid status may affect the dosage requirements for theophylline and digitalis. The doses of digitalis and theophylline may need to be reduced as thyroid function returns to normal.

Since propylthiouracil can cause hypothermia, extreme caution is required for patients receiving anticoagulants or heparin. Concurrent use of propylthiouracil with agranulocytosis producing medications may potentiate the risk of agranulocytosis.

#### **4.6 Fertility, Pregnancy and lactation**

##### Lactation

Propylthiouracil is present in breast milk in small amounts and neonatal development should be closely monitored in any nursing mother treated with this drug.

##### Pregnancy

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Propylthiouracil is able to cross the human placenta and can induce fetal goitre and hypothyroidism. Animal studies are insufficient with respect to reproductive toxicity. Epidemiological studies provide conflicting results regarding the risk of congenital malformations.

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, close maternal, foetal and neonatal monitoring is recommended.

##### Women of childbearing potential

Women of childbearing potential should be informed about the potential risks of propylthiouracil use during pregnancy.

#### **4.7 Effects on ability to drive and use machines**

Propylthiouracil has no documented effects on the ability to drive or use machines.

#### **4.8 Undesirable effects**

Minor adverse effects of propylthiouracil include: rash, urticaria, pruritus, abnormal hair loss, skin pigmentation, oedema, nausea, vomiting, epigastric distress, loss of taste, arthralgia, myalgia, paresthesia and headache.

Leucopenia is a common adverse effect, but it is usually mild and reversible.

Agranulocytosis is the most serious adverse effect of propylthiouracil, but the incidence is very low. It tends to occur within the first two months of therapy and patients over the age of 40 years and receiving larger doses are at greater risk.

Frequency unknown: Hepatitis, Hepatic Failure

Other severe, but infrequent adverse events include: aplastic anaemia; drug fever; lupus-like syndrome; severe hepatic reactions (including encephalopathy, fulminant hepatic necrosis and death); periarteritis; hypoprothrombinaemia; thrombocytopenia and bleeding.

Nephritis, interstitial pneumonitis, cutaneous and systemic vasculitis and polymyositis have also been reported.

Propylthiouracil-induced hepatotoxicity is rare and usually manifests as hepatocellular hepatitis with or without jaundice. Cholestatic jaundice has also occurred. Adverse liver effects are generally reversible on cessation of propylthiouracil.

#### **49      Overdose**

Symptoms of propylthiouracil overdose include: nausea, vomiting, epigastric distress, headache, fever, arthralgia, pruritus, oedema and pancytopenia, exfoliative dermatitis and hepatitis have occurred. Agranulocytosis is the most severe potential adverse effect due to acute propylthiouracil toxicity.

The treatment of propylthiouracil overdose should aim to minimise the amount of drug absorbed into the circulation.

Following acute toxicity the stomach should be emptied by gastric lavage or emesis. Activated charcoal may also be employed. General symptomatic and supportive measures should then be instituted. A full blood analysis should be considered because of the slight risk of haematological complications and appropriate therapy given if bone marrow depression develops.

There is no specific antidote for propylthiouracil.

### **5 PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Propylthiouracil blocks the production of thyroid hormones by inhibiting the enzyme thyroid peroxidase. This prevents the incorporation of iodine into tyrosyl residues of thyroglobulin and inhibits the coupling of the iodotyrosyl residues to form iodothyronine. It also interferes with the oxidation of iodide ion and iodotyrosyl groups.

Propylthiouracil does not inhibit the action or release of already formed thyroid hormone nor does it interfere with the effectiveness of circulating or exogenously administered thyroid hormone. It does, however, inhibit the peripheral de-iodination of thyroxine to tri-iodothyronine. Propylthiouracil also causes a gradual reduction in the level of circulating thyroid stimulating immunoglobulins in Grave's disease.

#### **5.2 Pharmacokinetic properties**

##### Absorption

Propylthiouracil is rapidly absorbed from the gastro-intestinal tract and has a bioavailability of 50-75%.

##### Half-Life

The elimination half-life of propylthiouracil is estimated to be 1-2 hours. The elimination half-life may be increased in hepatic and renal impairment and a dosage reduction may be warranted. Despite its short half-life, propylthiouracil is retained in the thyroid gland for at least 24 hours.

##### Distribution

Propylthiouracil appears to be concentrated in the thyroid gland. It readily crosses the placenta and is distributed into breast milk. About 80% of propylthiouracil is protein bound.

### Metabolism

Propylthiouracil undergoes rapid first-pass metabolism in the liver where it is metabolised to its glucuronic acid conjugate.

### Excretion

Propylthiouracil is mainly excreted in the urine as the glucuronic acid conjugate. Very little unchanged drug is excreted in the urine and negligible amounts are excreted in the faeces.

### **5.3 Preclinical safety data**

None stated.

## **6 PHARMACEUTICAL PARTICULARS**

6.1 List of excipients

Alginic acid ; Starch ; Lactose ; Magnesium stearate : Povidone

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Pigmented polypropylene containers fitted with a tamper evident closure containing 100 tablets

6.6 Special precautions for disposal

No special precautions are required.

## **7 Product licence holder**

ZIWELL MEDICAL (S) PTE LTD

1 UBI CRESCENT #05-03

SINGAPORE 40856

## **8 DATE OF REVISION OF THE TEXT**

November 20, 2020

