SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

PTU-50 (Propylthiouracil Tablet 50mg)

2. Qualitative and Quantitative Composition

Each tablet contains:

Propylthiouracil BP…..... 50mg

For Excipients see point 6.1

3. Pharmaceutical Form

Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Propylthiouracil tablets are indicated:

•In patients with Graves' disease with hyperthyroidism or toxic multinodular goiter who are intolerant of methimazole and for whom surgery or radioactive iodine therapy is not an appropriate treatment option.

•To ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy in patients who are intolerant of methimazole.

4.2 Posology and method of administration

Adults and elderly: Initially 300 to 600mg daily, once daily or in divided doses until the patient becomes euthyroid.

When the condition is controlled (usually after 1-2 months), the dose is reduced to 50 to 150mg daily and continued for 1-2 years.

In renal impairment: GFR 10 to 50ml/min, 75% dose

GFR < 10ml/min, 50% dose

In hepatic disease: Reduced dose

Children under 6 years: Not recommended

Children 6-10 years: Initially 50 to 150mg once daily or in divided doses

Children over 10 years: Initially 150 to 300mg once daily or in divided doses

4.3 Contraindications

Propylthiouracil is contraindicated in patients who have demonstrated hypersensitivity to the drug or any of the other product components.

Previous severe hypersensitivity reaction e.g. agranulocytosis, hepatitis, vasculitis, nephritis.

4.4 Special warnings and precautions for use

Liver Toxicity

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.

There are cases of liver injury, including liver failure and death, in women treated with propylthiouracil during pregnancy. Two reports of *in utero* exposure with liver failure and death of a newborn have been reported. The use of an alternative antithyroid medication (e.g., methimazole) may be advisable following the first trimester of pregnancy.

Biochemical monitoring of liver function (bilirubin, alkaline phosphatase) and hepatocellular integrity (ALT, AST) is not expected to attenuate the risk of severe liver injury due to its rapid and unpredictable onset. Patients should be informed of the risk of liver failure. Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.), particularly in the first six months of therapy. When these symptoms occur, propylthiouracil should be discontinued immediately and liver function tests and ALT and AST levels obtained.

Agranulocytosis

Agranulocytosis occurs in approximately 0.2% to 0.5% of patients and is a potentially life-threatening side effect of propylthiouracil therapy. Agranulocytosis typically occurs within the first 3 months of therapy. Patients should be instructed to immediately report any symptoms suggestive of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and

aplastic anemia (pancytopenia) may also occur. Propylthiouracil should be discontinued if agranulocytosis, aplastic anemia (pancytopenia), ANCA positive vasculitis, hepatitis, interstitial pneumonitis, fever, or exfoliative dermatitis is suspected, and the patient's bone marrow indices should be obtained.

Hypothyroidism

Propylthiouracil can cause hypothyroidism necessitating routine monitoring of TSH and free T4 levels with adjustments in dosing to maintain a euthyroid state. Because the drug readily crosses placental membranes, propylthiouracil can cause fetal goiter and cretinism when administered to a pregnant woman.

Precautions

General

Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, light colored stools, dark urine, right upper quadrant pain, etc.), particularly in the first six months of therapy. When these symptoms occur, measurement should be made of liver function (bilirubin, alkaline phosphatase) and hepatocellular integrity (ALT/AST levels).

Patients who receive propylthiouracil should be under close surveillance and should be counseled regarding the necessity of immediately reporting 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 obtained to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving concomitant drugs known to be associated with agranulocytosis.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants (Oral): Due to the potential inhibition of vitamin K activity by propylthiouracil, the activity of oral anticoagulants (e.g., warfarin) may be increased; additional monitoring of PT/INR should be considered, especially before surgical procedures.

Beta-adrenergic Blocking Agents: Hyperthyroidism may cause an increased clearance of beta blockers with a high extraction ratio. A reduced dose 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 dose of digitalis glycosides may be needed.

Theophylline: Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

4.6 Pregnancy and Lactation

Propylthiouracil may be given in pregnancy. It crosses the placenta and in high doses may cause foetal goitre and hypothyroidism, therefore the lowest possible dose should be given and thyroid function monitored every 4-6 weeks to maintain optimum control.

Propylthiouracil also transfers to breast milk but this does not preclude breast-feeding. Neonatal development and infant thyroid function should be closely monitored. The lowest effective dose should be used.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Blood and lymphatic system: Reversible leucopenia. Rarely, agranulocytosis, thrombocytopenia, leucopenia, aplastic anaemia, pancytopenia. A rare complication of therapy is a tendency to haemorrhage associated with hypoprothrombinaemia which may be controlled by the administration of phytomenadione.

Ear and labyrinth disorders: Rarely, hearing impairment may occur with propylthiouracil. The impairment usually becomes less marked after withdrawal of the drug.

Gastrointestinal: Nausea, gastrointestinal disturbances, taste perversion. Rarely vomiting.

General: Fever.

Hepatobiliary: Jaundice (usually cholestatic), hepatic necrosis (sometimes with fatal consequences), encephalopathy. More commonly, asymptomatic liver

function test abnormalities (increased serum bilirubin, Alanine transaminase and / or alkaline phosphatase concentrations), which are reversible on dose reduction or discontinuation of treatment, may occur with propylthiouracil.

Frequency unknown: Hepatitis, hepatic failure.

Immune system: Interstitial pneumonitis, alveolar haemorrhage, lymphadenopathy, arthritis, nephritis, vasculitis and lupus erythematosus-like syndromes hasve occurred in some patients taking thiourea antithyroid drugs. An immune mechanism has been proposed. There have also been rare reports of acute glomerulonephritis. Hypersensitivity reactions may also be associated with the development of antineutrophil cytoplasmic antibodies (ANCA).

Musculoskeletal: Myopathy, arthralgia,

Nervous system: Headache.

Skin: Mild papular skin rashes, pruritus, urticaria, alopecia, cutaneous vasculitis.

4.9 Overdose

Symptoms: Goitre and hypothyroidism may be induced by repeated over dosage. Single overdose is not dangerous. Overdose may manifest as vomiting, epigastric distress, headache, fever, arthralgia, pruritus, and pancytopenia.

Treatment: The treatment of propylthiouracil overdose should aim to minimise the amount of drug absorbed into the circulation. Treatment should involve liberal use of oral fluids. 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 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 inhibits the conversion of thyroxine to triiodothyronine in peripheral tissues and may therefore be an effective treatment for thyroid storm.

Propylthiouracil is readily absorbed and is extensively metabolized. Approximately 35% of the drug is excreted in the urine, in intact and conjugated forms, within 24 hours.

5.2 Pharmacokinetic properties

Propylthiouracil is rapidly absorbed from the gut with average peak blood levels about one hour after administration of an oral dose. Between half and three quarters of the oral dose is bioavailable, due to incomplete absorption or rapid first pass metabolism by the liver. Most is excreted as the glucuronic acid conjugate in the urine. Plasma half life is 1-3 hours, the volume of distribution approximately 30l, with about 80% plasma protein binding.

Propylthiouracil crosses the placenta and is secreted in breast milk reaching about 10% of the serum concentration.

5.3 Preclinical safety data

There has been no systematic long term animal toxicology studies performed. Some short term studies carried out when this class of drugs was introduced (approx 45 years ago) show that rats and rodents treated with high doses of propylthiouracil and made markedly hypothyroid will frequently develop thyroid hyperplasia, adenomas, carcinoma, pituitary adenomas and parathyroid hyperplasia.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose anhydrous, Maize starch, Purified talc, Sodium Starch Glycolate, Povidone, Magnesium Stearate

6.2 Incompatibilities

None

6.3 Shelf life

36 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store in a well closed container. Below 25°C. Protect from light.

6.5 Nature and contents of container

100 Tablets packed in 43ml HDPE opaque milky white container with closure in a carton along with pack insert.

6.6 Special Precaution for disposal

None.

7. Supplier

Macleods Pharmaceuticals Ltd.

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8. Market authorization number

05389/07530/NMR/2019

9. Date of first authorization/ last renewal

Oct 1, 2020

10. Date of Revision of the Text:

References:

1]http://www.medicines.org.uk/emc/medicine/27760/SPC/Propylthiouracil+50mg+Tablets/

2]http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a57c49ae-d659-49fa-84e3-cf6d1f9e6f97

3] http://dailymed.nlm.nih.gov/dailymed/ archives /fdaDrugInfo.cfm?archiveid=16211