Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Propylthiouracil 50 mg Tablets

propylthiouracil

PL 33831/0041

BLUE BIO PHARMACEUTICALS LIMITED

LAY SUMMARY

Propylthiouracil 50 mg Tablets
propylthiouracil

This is a summary of the Public Assessment Report (PAR) for Propylthiouracil 50 mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Propylthiouracil 50 mg Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Propylthiouracil 50 mg Tablets and what are they used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Propylthiouracil Tablets BP 50 mg.

Propylthiouracil 50 mg Tablets are used in the treatment of hyperthyroidism. Hyperthyroidism is where an overactive thyroid gland produces too much thyroid hormone. They are also used to treat Graves' disease, thyrotoxicosis and thyrotoxic crisis (when levels of thyroid hormone are dangerously high).

Propylthiouracil 50 mg Tablets may also be given to lower very high levels of thyroid hormone before surgery or radioactive iodine treatment. Children may be given Propylthiouracil 50 mg Tablets to delay the need for surgery (or other treatment to remove part of an overactive thyroid gland).

How do Propylthiouracil 50 mg Tablets work?
The active substance in Propylthiouracil tablets is propylthiouracil. This medicine blocks the production of thyroid hormones by inhibiting the enzyme thyroid peroxidase.

How are Propylthiouracil 50 mg Tablets used?
The pharmaceutical form of this medicine is tablets and the route of administration is oral (by mouth). The tablets should be swallowed whole with water.

The doctor may want the patient to have regular blood tests or other tests to check their condition and to make sure that they are taking the right dose. The following doses are intended as a guide.

<u>For adults in management of hyperthyroidism and prior to surgery</u>
The starting dose is between 300 mg and 600 mg a day (6 to 12 tablets), taken as a single dose or in divided doses. This may be gradually reduced to between 50 mg and 150 mg (1 to 3 tablets) daily as the patient's condition improves.

<u>For adults in preparation for radioactive iodine therapy</u>
The dose is as above and should be taken for several weeks prior to radioactive iodine therapy. Treatment should be stopped 2 to 4 days before iodine treatment.

For adults in thyrotoxic crisis
The dose is 200 mg (4 tablets) every 4 to 6 hours for the first 24 hours. This is then reduced as the condition improves. Elderly patients will be given the adult dose mentioned above. Patients with liver or kidney problems may be given a lower dose

CHILDREN

- Aged 6 to 10 years: The starting dose is 50 mg to 150 mg a day (1 to 3 tablets)
- Aged over 10 years: The starting dose is 150 mg to 300 mg a day (3 to 6 tablets).
- Neonates (babies less than 4 weeks old): The dose will be worked out depending on the baby's weight. The usual daily dose is 5 mg to 10 mg for each kilogram of body weight

For further information on how Propylthiouracil 50 mg Tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Propylthiouracil 50 mg Tablets have been shown in studies?
Propylthiouracil 50 mg Tablets is a generic medicine that fulfils criteria meaning that no additional studies are required. Propylthiouracil 50 mg Tablets has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Propylthiouracil 50 mg Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Propylthiouracil 50 mg Tablets is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Propylthiouracil 50 mg Tablets approved?
It was concluded that, Propylthiouracil 50 mg Tablets has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Propylthiouracil 50 mg Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Propylthiouracil 50 mg Tablets. The RMP details the important risks of Propylthiouracil 50 mg Tablets, how these risks can be minimised, any uncertainties about Propylthiouracil 50 mg

Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Propylthiouracil 50 mg Tablets:

Summary of safety concerns	
Important identified risks	• Hepatotoxicity • Vasculitis • Agranulocytosis • Hypothrombinaemia • Hypothyroidism
Important potential risks	• None
Missing information	• Safety in Lactation

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Propylthiouracil 50 mg Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Propylthiouracil 50 mg Tablets
A marketing authorisation for Propylthiouracil 50 mg Tablets was granted in the United Kingdom (UK) on 23 May 2024.

The full PAR for Propylthiouracil 50 mg Tablets follows this summary.

This summary was last updated in January 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Propylthiouracil 50 mg Tablets (PL 33831/0041) could be approved.

The product is approved for the following indications:

- management of hyperthyroidism, including the treatment of graves' disease and thyrotoxicosis.
- amelioration of hyperthyroidism in preparation for surgical treatment.
- an adjunct to radioactive iodine therapy.
- in juvenile hyperthyroidism to delay ablative therapy
- to manage thyrotoxic crisis.

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.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Propylthiouracil Tablets BP 50 mg that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required and no new clinical studies were provided with this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 6 December 2018. Following provision of additional data, the commission were reassured on the quality of the product.

A marketing authorisation for Propylthiouracil 50 mg Tablets was granted in the United Kingdom (UK) on 23 May 2024.

II QUALITY ASPECTS

II.1 Introduction

The product consists of 50 mg of propylthiouracil.

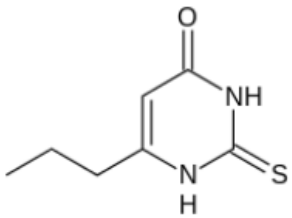
In addition to propylthiouracil, this product also contain the excipients lactose monohydrate, sodium starch glycolate, povidone (Kollidon-30), microcrystalline cellulose, pregelatinised starch, silica colloidal anhydrous and magnesium stearate.

The finished product is packaged in PVC/PVDC - aluminium blister pack containing 56 or 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: propylthiouracil
Chemical Name: 2,3-Dihydro-6-propyl-2-thioxo-4(1H)-pyrimidinone
Molecular Formula: $C_7H_{10}N_2OS$



Chemical Structure:
Molecular Weight: 170.23 g mol^{-1}
Appearance: White or almost white, crystalline powder or crystals
Solubility: Very slightly soluble in water, sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides

The information related to the active substance was provided in an ASMF.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months (2 years), with no special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of propylthiouracil are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version(s) of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of propylthiouracil is well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics
No new pharmacokinetic data were submitted for this application and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Propylthiouracil Tablets BP 50 mg.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with propylthiouracil is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**