Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Propylthiouracil 50 mg Tablets
Propylthiouracil 100 mg Tablets

(propylthiouracil)

PL 20117/0382-0383

Morningside Healthcare Limited

LAY SUMMARY

Propylthiouracil 50 mg Tablets
Propylthiouracil 100 mg Tablets
(propylthiouracil)

This is a summary of the Public Assessment Report (PAR) for Propylthiouracil 50 mg and 100 mg Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Propylthiouracil tablets in this lay summary for ease of reading.

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

What are Propylthiouracil tablets and what are they used for?
The application for Propylthiouracil 50 mg tablets is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the United Kingdom (UK) called Propylthiouracil Tablets BP 50 mg.

The application for Propylthiouracil 100 mg tablets is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the UK called Propylthiouracil Tablets BP 50 mg, albeit with certain differences. In this case, the difference between Propylthiouracil 100 mg Tablets compared to the reference product is a change in strength of the active substance. Propylthiouracil 100 mg Tablets are a higher strength of the active substance than the reference product.

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

How do Propylthiouracil 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 tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (taken by mouth). The patient should swallow the tablets whole with water.

The dose will be on the pharmacist's label. The patient should check the label carefully. It should tell you how many tablets to take and how often.

The patient's doctor may request their patient has 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:

Adults:
For management of hyperthyroidism and prior to surgery:
The starting dose is between 300 mg and 600 mg a day, taken as a single dose or in divided doses. This may be gradually reduced to between 50 mg and 150 mg daily as the patient's condition improves.

In preparation for radioactive iodine therapy: 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 thyrotoxic crisis: The dose is 200 mg 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.
Aged over 10 years: The starting dose is 150 mg to 300 mg a day.

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 tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

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

What benefits of Propylthiouracil tablets have been shown in studies?
As Propylthiouracil tablets are generic/hybrid medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent/therapeutically equivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Propylthiouracil tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs 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 these medicines. Patients can also report suspected side effects themselves, or a report can be made on behalf of the patient by someone else who cares for them, directly via the Yellow Card scheme at www.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 these medicines.

As Propylthiouracil tablets are generic/hybrid medicines and are bioequivalent/ therapeutically equivalent to the reference medicine, their possible side effects are considered to be the same as the reference medicine.

Why were Propylthiouracil tablets approved?
It was concluded that, Propylthiouracil tablets have been shown to be comparable to and to be bioequivalent/therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that Propylthiouracil tablets can be approved for use.

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

Table 1: Summary of safety concerns

Summary of safety concerns*	
Important identified risks	• Hepatotoxicity • Agranulocytosis • Vasculitis • Hypothrombinaemia • Hypothyroidism
Important potential risk	• Use in pregnancy
Missing information	• Use in Lactation

The information included in the SmPCs 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 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 these applications and are satisfactory.

Other information about Propylthiouracil tablets
Marketing Authorisations for Propylthiouracil tablets were granted in the UK on 10 March 2022.

The full PAR for Propylthiouracil tablets follows this summary.

This summary was last updated in May 2022.

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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 applications for Propylthiouracil 50 mg and 100 mg Tablets (PL 20117/0382-0383) could be approved.

The products are approved for the following indications:
1. Management of hyperthyroidism, including the treatment of Graves' disease and thyrotoxicosis.
2. Amelioration of hyperthyroidism in preparation for surgical treatment.
3. An adjunct to radioactive iodine therapy.
4. In juvenile hyperthyroidism to delay ablative therapy.
5. To manage thyrotoxic crisis.

The active substance, 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.

The application for Propylthiouracil 50 mg Tablets was approved under Regulation 51B of The Human Medicines Regulations 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 within the United Kingdom (UK) for a suitable time, in line with the legal requirements.

The application for Propylthiouracil 100 mg Tablets was approved under Regulation 52B of The Human Medicines Regulations 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Propylthiouracil Tablets BP 50 mg.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic/hybrid medicinal products of a suitable reference product. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

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

National Marketing Authorisations were granted in the UK on 10 March 2022.

II QUALITY ASPECTS

II.1 Introduction

These products contain 50 mg or 100 mg of propylthiouracil in each tablet.

In addition to propylthiouracil, these products also contain the excipients starch, pregelatinized; lactose monohydrate; sodium starch glycolate (Type-A); povidone K-30 and magnesium stearate.

The finished product are packaged in aluminium-aluminium blisters, in pack sizes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120 or 500 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.

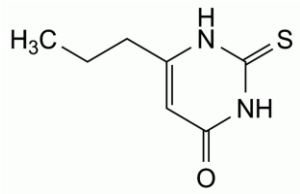
II.2 ACTIVE SUBSTANCE

rINN: Propylthiouracil

Chemical Name: 2,3-dihydro-6-propyl-2-thioxopyrimidin-4(1*H*)-one

Molecular Formula: $C_7H_{10}N_2OS$

Chemical Structure:



Molecular Weight: 170.2 g/mol

Appearance: White or almost white crystalline powder or crystals.

Solubility: Propylthiouracil is very slightly soluble in water, sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides.

Propylthiouracil is the subject of a European Pharmacopoeia monograph.

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 PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been 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 have been 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 products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

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

Satisfactory batch formulation data have been provided for the manufacture of the products, 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 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 Marketing Authorisations is 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic/hybrid versions of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology, efficacy and safety of propylthiouracil are well-known. With the exception of data one bioequivalence study, no new clinical data are provided or are required for applications of these types. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study.

Bioequivalence study (single-dose, fasting conditions)
This study was a randomised, open-label, analyst blind, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study comparing the test product Propylthiouracil 100 mg Tablets versus the reference product Propylthiouracil Tablets BP 50 mg in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least ten hours, subjects were administered a single oral dose (100 mg) of either the test (1 x 100 mg tablet) or reference product (2 x 50 mg tablets) with approximately 240 ml water. Blood samples were taken pre-dose and up to 12 hours post-dose, with a washout period of four days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Pharmacokinetic parameters for propylthiouracil

Parameters (units)	Least Square Means		Geometric Least Square Means		Ratio (%) (T Vs R)	90% Confidence Intervals (%)	Intra Subject CV (%)	Power (T Vs R) (%)
	T	R	T	R				
Ln (C_{max}) (ng/mL)	7.9064	7.8707	2714.667	2619.341	103.64	96.17 - 111.69	22.09	99.91
Ln (AUC_t) (hr *ng/mL)	8.7503	8.7775	6312.591	6486.824	97.31	94.32 - 100.41	9.15	100.00

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the 50 mg strength of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 100 mg product strength can be extrapolated to the 50 mg strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 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 Marketing Authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

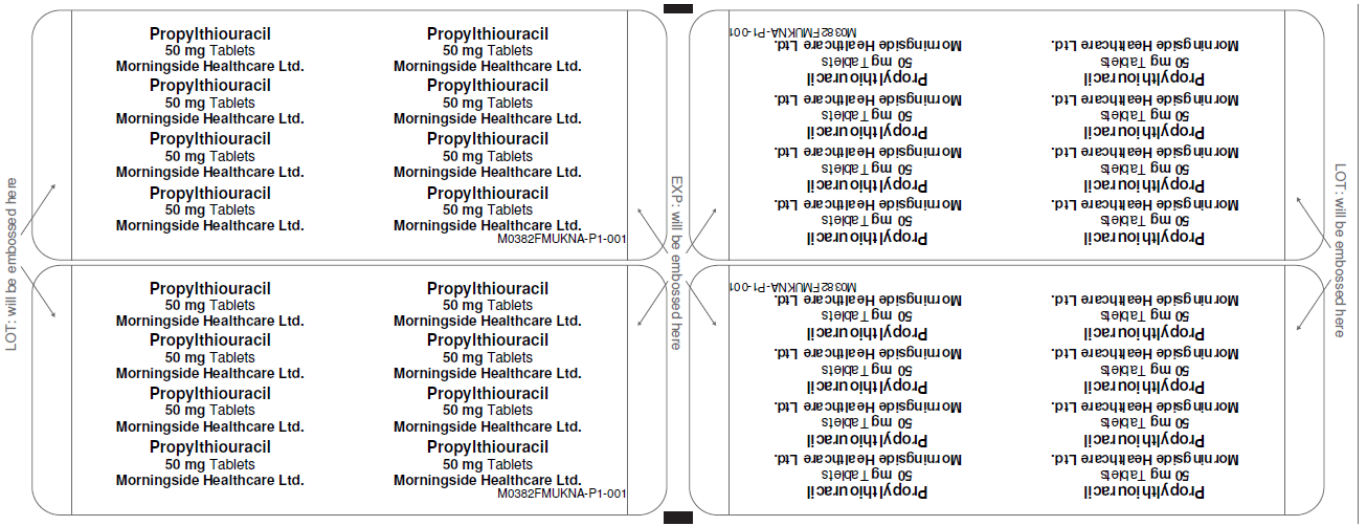
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with propylthiouracil is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

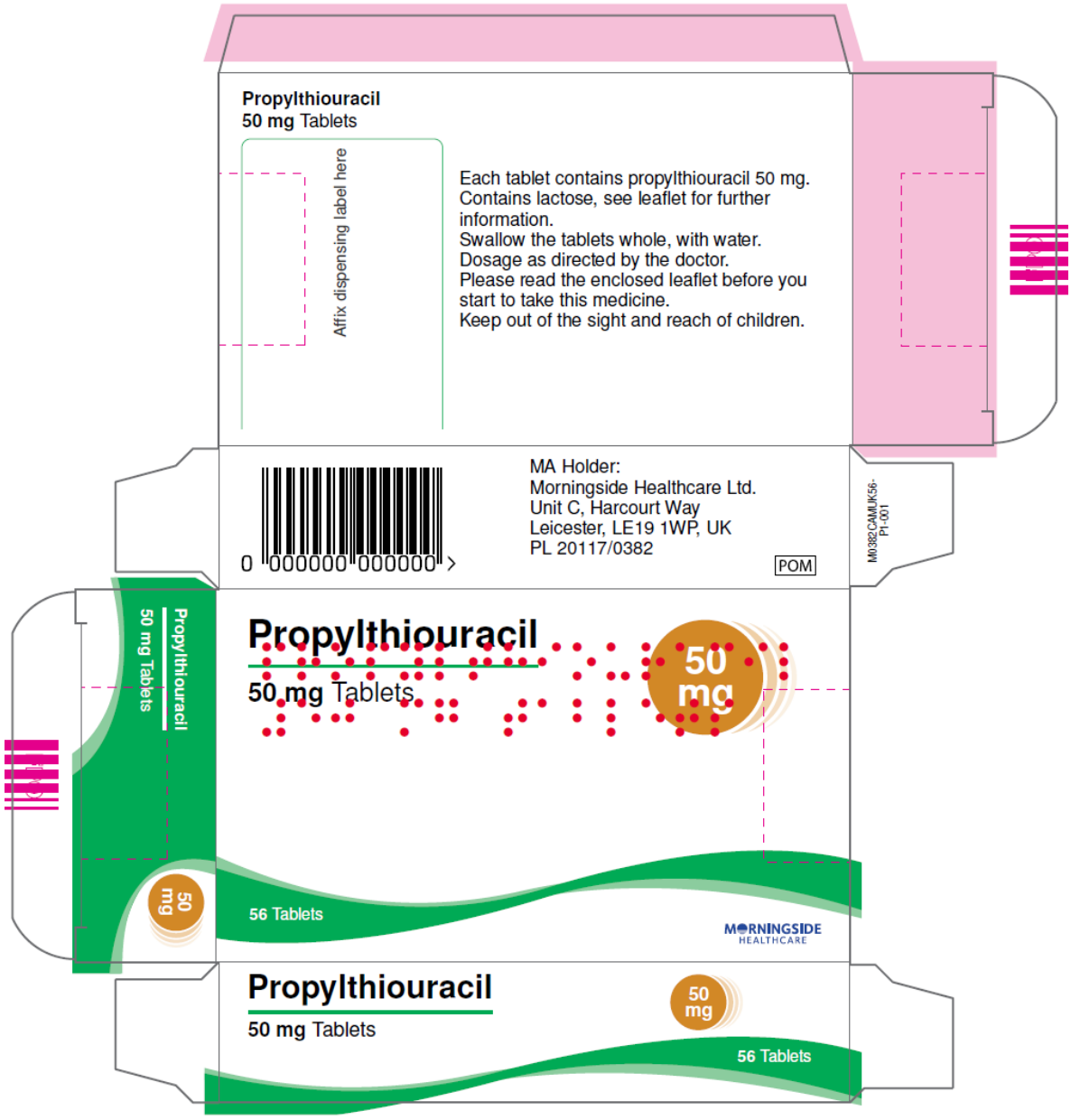
The Summaries of Product Characteristics (SmPCs), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

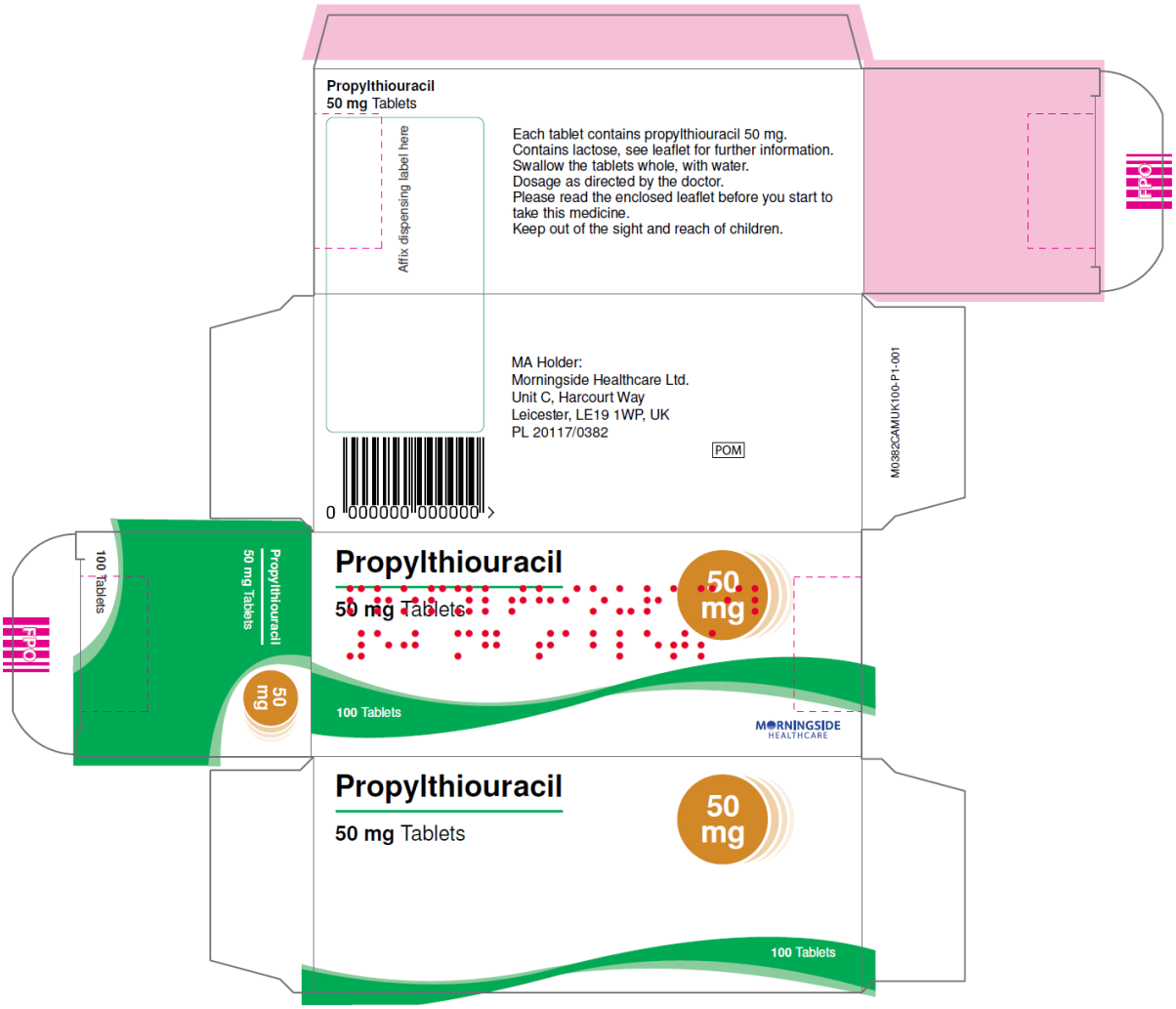
In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

Propylthiouracil 50 mg Tablets






Propylthiouracil
50 mg Tablets
Affix dispensing label here
Each tablet contains propylthiouracil 50 mg.
Contains lactose, see leaflet for further information.
Swallow the tablets whole, with water.
Dosage as directed by the doctor.
Please read the enclosed leaflet before you start to take this medicine.
Keep out of the sight and reach of children.
FPO
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
PL 20117/0382
POM
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Propylthiouracil
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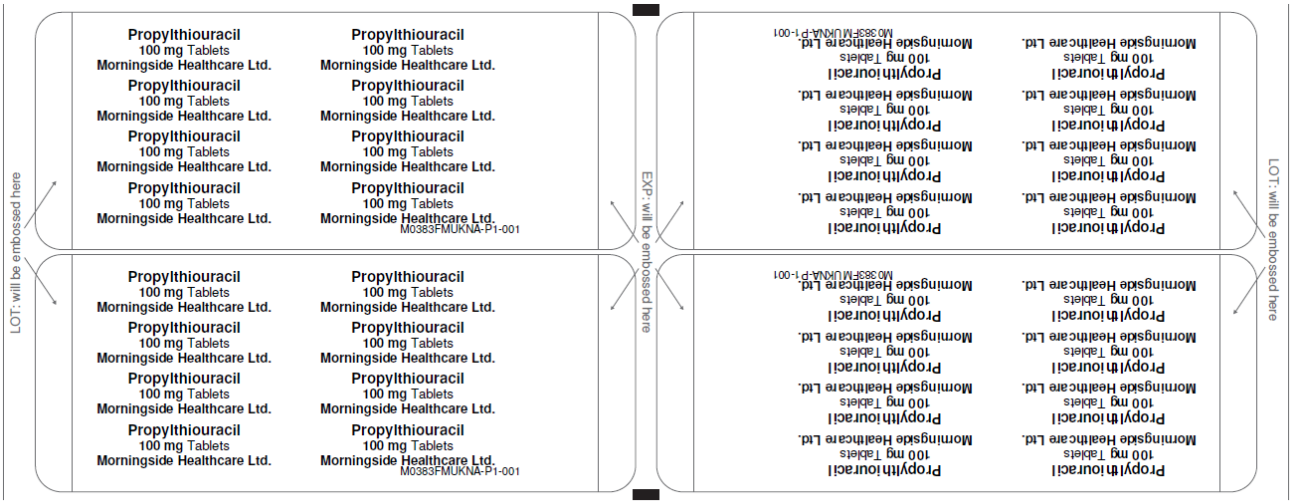
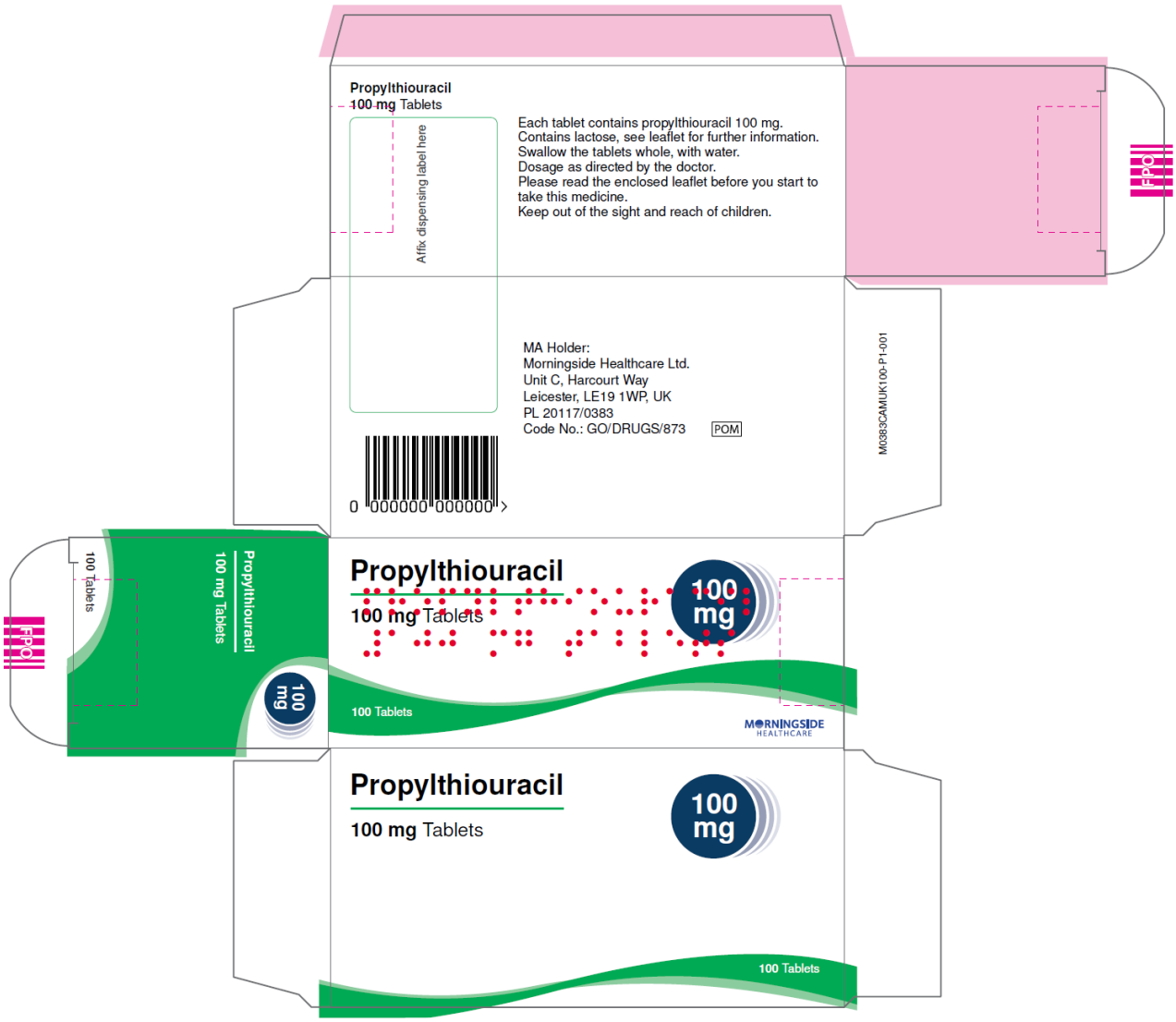
Propylthiouracil 100 mg Tablets





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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 Authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

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