Public Assessment Report

Decentralised Procedure

Propylthiouracil 50 mg Tablets

Propylthiouracil

UK/H/5393/001/DC

UK licence no: PL 00042/0205

Halewood Chemicals Limited
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Propylthiouracil 50 mg Tablets (PL 00042/0205 - 0001; UK/H/5393/001/DC). It explains how Propylthiouracil 50 mg Tablets 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 this product.

The product will be referred to as Propylthiouracil Tablets throughout the remainder of this PAR.

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?
Propylthiouracil Tablets are used to treat hyperthyroidism: a condition where the thyroid gland is overactive and makes too much thyroxine. Thyroxine is carried around the body in the bloodstream. It helps to keep the body's functions (the metabolism) working at the correct pace. Many cells and tissues in the body need thyroxine to keep them working correctly. If your thyroid gland makes too much thyroxine it can cause many of your body's functions to speed up. As a result you may suffer from side effects such as being restless all the time, feeling nervous, irritable, sleeping poorly and always being “on the go”, shaky hands, losing weight, sweating, shortness of breath, feeling tired all the time, and other effects.

This medicine is used to treat an overactive thyroid gland (hyperthyroidism) in adults (including the elderly), and in children and adolescents aged 6 to 18 years.

This medicine helps restore thyroxine levels in your bloodstream to normal levels: It may take several weeks for this to happen. Hence it is important to keep taking the medicine every day.

How do Propylthiouracil Tablets work?
Propylthiouracil Tablets contain the active substance propylthiouracil. This is an antithyroid medicine that reduces your body’s ability to make thyroxine, a body chemical (hormone) that is made by the thyroid gland in your neck and helps to regulate growth and metabolism.

Each tablet contains 50 mg of Propylthiouracil.

How are Propylthiouracil Tablets used?
Propylthiouracil Tablets can be taken with or without food. The tablets should be swallowed with a drink of water. The tablets should be taken at the same time each day, unless the prescribing doctor has recommended otherwise.

In adult and elderly patients the recommended starting dose is 300 to 600 mg daily (6 to 12 tablets), taken as recommended by his/her doctor.

In children aged over 10 years, the recommended starting dose is 150 to 300 mg daily (3 to 6 tablets), taken as recommended his/her doctor.

In children aged six to ten years, the recommended starting dose is 50 to 150 mg daily (1 to 3 tablets), taken as recommended his/her doctor.

Propylthiouracil Tablets is not recommended for use in children under 6 years of age.
In patients with kidney or liver disease, his/her doctor will reduce the dose according to the condition.

If you accidentally take too many tablets contact your doctor or pharmacist or nearest hospital casualty department immediately. Take this leaflet and any remaining tablets with you to show the doctor or pharmacist.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

**What benefits of Propylthiouracil Tablets have been shown in studies?**
The active ingredient propylthiouracil has well-established use and have been available in the European Union for many years.

The company provided bibliographic data on the efficacy and safety for this well-established combination. These data have shown that Propylthiouracil Tablets are effective in treating the condition for which it is authorised.

**What are the possible side effects of Propylthiouracil Tablets?**
For information about side effects that may occur when using Propylthiouracil Tablets, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why are Propylthiouracil Tablets approved?**
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Propylthiouracil Tablets outweigh the identified risks, and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Propylthiouracil Tablets?**
A Risk Management Plan (RMP) has been developed to ensure that Propylthiouracil Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Propylthiouracil Tablets**
Following the completion of a decentralised procedure a Marketing Authorisation was granted in the UK on 22 December 2016. The full PAR for Propylthiouracil Tablets follows this summary.

For more information about treatment with Propylthiouracil Tablets, read the PIL or contact your doctor or pharmacist.

This summary was last updated in February 2017.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Propylthiouracil Tablets (PL 00042/0205; UK/H/5393/001/DC) could be approved.

This is a decentralised complex abridged application submitted under Article 10a (a well-established use application) of Directive 2001/83/EC, as amended. The United Kingdom acted as RMS and Ireland as the CMS.

Propylthiouracil is an anti-thyroid drug that has been in clinical use for the oral treatment of hyperthyroidism since the 1940s. The main mode of action of propylthiouracil in the treatment of hyperthyroidism is inhibition of the synthesis of thyroid hormones. Following absorption, the drug is concentrated in the thyroid gland, which is its primary site of activity. Its duration of activity is more closely related to its concentration in the thyroid gland than its plasma half-life. It works primarily by interfering with the synthesis of the iodine-containing hormones thyroxine (T4) and tri-iodothyronine (T3) via inhibition of peroxidase in the thyroid gland. It appears to interfere with peroxidase-mediated incorporation of iodine into tyrosyl residues of the precursor thyroglobulin. It also inhibits the coupling of these iodotyrosyl residues to form iodothyronines. There is some evidence that the coupling reaction is more sensitive than the iodination reaction to the inhibitory effects of propylthiouracil.

The application is for a Prescription-Only Medicine (legal status “POM”).

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is application is submitted under Article 10a of Directive 2001/83/EC (well-established use). The applicant has not undertaken any clinical studies, but provided comprehensive biopharmaceutical data to bridge the product to bibliographic data. From the data provided, it is considered that the formulation of the product may not have a significant effect on bioavailability. The efficacy, safety and risk/benefit of this product have been determined by published literature.

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

All Member States agreed to grant licences for the above products at the end of procedure (Day 210 – 15 December 2016). After a subsequent national phase, the UK granted a licence for this product on 22 December 2016 (PL 00042/0205).
II QUALITY ASPECTS

II.1 Introduction
This decentralised abridged application is submitted by Halewood Chemicals Limited under Article 10a (well-established use or bibliographic) of Directive 2001/83/EC, as amended.

Propylthiouracil Tablets contain 50 mg of propylthiouracil per tablet. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, spray-dried acacia, croscarmellose sodium, sodium laurilsulfate and magnesium stearate.

The finished product is packed in either:
1. white polypropylene bottles fitted with a tamper-evident high-density polyethylene (HDPE) cap, in pack sizes of 100 tablets
2. opaque polyvinylchloride/polyvinylidene chloride (PVC/PVDC) aluminium foil blisters, in pack sizes of 28 or 56 tablets.

Not all pack sizes may be marketed.

All primary product packaging complies with EU legislation concerning materials in contact with foodstuffs.

II.2 DRUG SUBSTANCES

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

Structure:

H₃C
\[ \text{N} \]
\[ \text{S} \]
\[ \text{H} \]
\[ \text{O} \]
\[ \text{N} \]

Molecular Formula: C₇H₁₀N₂OS

Molecular Weight: 170.2

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.

Propylthiouracil is the subject of a European Pharmacopoeia (Ph.Eur) monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.
Propylthiouracil 50 mg Tablets

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 specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning 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
The objective of the development programme was to formulate safe, efficacious, tablets containing 50 mg of propylthiouracil per tablet.

A satisfactory level of detail was provided in relation to the pharmaceutical development.

All the excipients comply with the appropriate monographs in the Ph. Eur. and the product manufacturer will be using pharmacopoeial methods to test the materials.

None of the excipients are of human or animal origin and furthermore, none are sourced from genetically modified organisms.

There were no novel excipients used.

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

Satisfactory batch formula have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and are adequately validated. Batch data have been provided that comply with the release specification.

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 3 years with a storage condition ‘Store in the original package in order to protect from light’ is set. This is satisfactory.

Suitable post approval stability commitments have been provided to continue stability testing on batches of the finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation 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.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Propylthiouracil is a thionamide (thiourea) antithyroid drug that is used for the management of hyperthyroidism. It works primarily by interfering with the synthesis of the iodine-containing hormones thyroxine (T4) and tri-iodothyronine (T3) via inhibition of peroxidase in the thyroid gland. It appears to interfere with peroxidase-mediated incorporation of iodine into tyrosyl residues of the precursor thyroglobulin. It also inhibits the coupling of these iodotyrosyl residues to form iodothyronines. There is some evidence that the coupling reaction is more sensitive than the iodination reaction to the inhibitory effects of propylthiouracil.

Unlike other thionamides, propylthiouracil also partially inhibits the peripheral deiodination of thyroxine (T4) to the active form tri-iodothyronine (T3), thereby reducing T3 formation in the liver and many other tissues. This secondary mode of action is more important in cases of severe hyperthyroidism than in the treatment of mild disease states.

Reductions in serum T4 and T3 levels were seen in male Sprague-Dawley rats following repeated oral doses of propylthiouracil 0.01 or 1 mg/kg daily for 28 or 30 days. The higher dose was also associated with increased serum thyroid-stimulating hormone (thyrotropin, TSH) levels, increased weights of the thyroid gland and pituitary gland, hypertrophy of follicular epithelial cells in the thyroid gland and an increase in basophilic cells in the pituitary gland in comparison with controls.

Similarly, repeated daily doses of propylthiouracil 5 mg/kg for up to 21 days led to significant reductions in serum total T3 and T4 levels and increased serum levels of TSH from day six onwards in rats.

In another study, oral administration of propylthiouracil to rats for seven or 14 days led to reductions in serum T4 and T3 and a massive increase in serum TSH levels with hypertrophy of the thyroid gland. The effects were considered to be primarily due to reductions in the synthesis or secretion of thyroid hormones from the thyroid gland.

Propylthiouracil also caused reductions in hepatic 5’- deiodinase activity in vitro and in vivo in the rats. The inhibitory effect on iodination mechanisms in the thyroid appears to be prolonged; 18 hours after the injection of a small dose of propylthiouracil, iodination in the thyroid gland remained inhibited by more than 90 %. Prolonged inactivation of thyroid peroxidase by low doses of propylthiouracil was also demonstrated in vitro and in vivo in an earlier study in rats.
Inhibition of peripheral conversion of T4 to T3 has been studied in thyroidectomised, hypothyroid rats treated with thyroxine with or without intraperitoneal propylthiouracil 10 mg / kg body weight daily for 5-15 days. Treatment with propylthiouracil led to higher serum T4, lower serum T3 and increased serum TSH levels. Analysis of liver mitochondrial α-GPD activity during maintenance therapy with T3 indicated no inhibition of the biological response of propylthiouracil to T3.

The effects of prolonged oral administration of propylthiouracil on peripheral conversion of T4 to T3 were later studied in thyroxine-maintained athyreotic rats. The drug reduced the metabolic clearance rates of both T4 and T3 and reduced T3 levels in the plasma, muscle, liver, kidney and cerebellum. Intracellular concentrations of T3 in the cerebral cortex were unaffected and even increased in the pituitary gland. The amount of T3 derived from local conversion from T4 was reduced in the liver. Propylthiouracil did not affect the conversion of T4 to T3 in the cerebellum, but increased the amount of T3 derived from T4 in the cerebral cortex and pituitary gland. The results indicate that, unlike in the liver, local production of T3 in the brain and pituitary is not inhibited by propylthiouracil.

Administration of high-dose propylthiouracil 50 mg/kg body weight for seven days led to marked reductions in hepatic T4 and T3 levels in rats. The activity of the microsomal ethanol oxidising system was increased, although the activities of alcohol dehydrogenase and catalase remained unchanged. Induction of a hyperthyroid hepatic state led to a similar increase in the activity of the microsomal ethanol oxidising system, with a reduction in alcohol dehydrogenase activity but unchanged catalase activity. It was concluded that induction of the microsomal system by high-dose propylthiouracil was independent of its action on thyroid hormones.

Several published studies of the pharmacological activity of propylthiouracil other than its effect on the thyroid gland are available. It has been shown to potentiate glucose-induced secretion of insulin from rat pancreatic islet cells in vitro, possibly by increasing islet cyclic AMP levels. It demonstrated both inhibitory and stimulatory effects on the production of progesterone and its precursor, pregnenolone, in rat granulosa cells, possibly by an effect on negative feedback mechanisms. Propylthiouracil also inhibited production of testicular testosterone in rats and monkeys. Suggested mechanisms included inhibition of the conversion of cholesterol to pregnenolone in rats or inhibition of 17β-hydroxysteroid dehydrogenase and post cyclic-AMP pathways in monkeys.

Propylthiouracil induced endothelium-dependent vasodilatation in a study in rabbits. A similar effect was seen in patients with hyperthyroidism as described in the clinical overview. The mechanism was thought to be independent of its effect on thyroid hormones and to be mediated by nitric oxide. The potentially beneficial effect on atherosclerosis could be due, at least in part, to increased differentiation of vascular smooth muscle cells by propylthiouracil. Propylthiouracil appears to have antioxidant properties. It also suppresses the mitogenic activation of lymphocytes but does not appear to have local anaesthetic activity. It has been suggested that propylthiouracil may have some immunosuppressant activity by acting as a modulator of both the cellular immune response and antibody production. Propylthiouracil was found to alter the activity of the alternative pathway of complement in a study in rats.
III.4 Pharmacokinetics

Absorption and bioavailability

Propylthiouracil is well absorbed after oral administration. Peak plasma concentrations are attained 1-2 hours after oral administration. Significant differences in the solubility profiles of different oral propylthiouracil formulations have been reported. The absorption of propylthiouracil from two generic formulations, representing the extremes of solubility from 12 products tested, was assessed in euthyroid, hypothyroid and hyperthyroid beagle dogs. The rates of absorption were found to vary appreciably between products. This variability can likely be attributed to: the complexity of the natural regulation of thyroid function, the wide inter-individual variations in therapeutic response to propylthiouracil, the gradual onset of its pharmacological effect and the general need for long-term treatment to achieve an optimum response, therefore, the differences in the bioavailability of different oral formulations of propylthiouracil will have little clinical significance with respect to the efficacy of treatment. Similarly, the risk of inducing hypothyroidism should be adequately controlled by routine monitoring of serum thyroid hormone levels.

Distribution

Propylthiouracil is concentrated in the thyroid gland by an active transport mechanism. Accumulation and retention of radiolabelled propylthiouracil in the thyroid gland of rats has been demonstrated. At low doses, thyroid concentrations of propylthiouracil significantly exceed serum concentrations in rats. Marked inhibition of the intrathyroid metabolism of the drug with increasing doses implied that that it inhibits its own intrathyroid metabolism.

Radiolabelled propylthiouracil also accumulated in the mouse thyroid gland in vivo, with maximal tissue/plasma ratios and maximal intrathyroidal levels of the labelled drug seen at the lowest dose studied (0.1 μg/animal). Pre-treatment with sodium perchlorate 10 mg (but not higher doses) abolished iodine trapping by the thyroid gland and reduced the accumulation of propylthiouracil. This suggests that accumulation of the drug in the thyroid does not depend directly on the anion trap and may depend on subsequent metabolism in the gland.

Radiolabelled propylthiouracil also accumulated in the mouse submandibular gland in vivo, with maximal tissue/plasma ratios seen at the lowest dose studied (0.1 μg/animal). Drug accumulation persisted when iodine trapping was inhibited using sodium perchlorate. This suggests that drug accumulation in the submandibular gland is not dependent on the anion trap. Accumulation at the site of peroxidase activity in the gland indicated that this might be an important factor in the mechanism of accumulation and possibly related to subsequent drug metabolism.

Propylthiouracil is about 75% - 80 % protein bound in humans. Non-covalent protein binding has also been demonstrated in rats. The drug crosses the placenta and appears in breast milk in low concentrations.

Metabolism

Metabolism of propylthiouracil probably occurs in the liver. In humans more than 50 % of a dose is excreted as the glucuronic acid conjugate. The major urinary metabolite in rats and mice is also the glucuronide. Intrathyroid metabolites of propylthiouracil detected in an in vitro model system containing thyroid peroxidise included the disulphide, sulphate/sulphite and sulphinate.
Excretion
Propylthiouracil is excreted in the urine as unchanged drug (less than 2% of an administered dose in humans) and metabolites. The elimination half-life is about 1-3 hours in humans.

Pharmacokinetic drug interactions
Displacement experiments have shown interactions of propylthiouracil with other protein-bound drugs such as aspirin, warfarin and phenylbutazone, although not with antipyrine, nortriptyline or other basic drugs.

Conclusions on pharmacokinetics
Propylthiouracil is well-established, having been used clinically for many years and the existence of large amounts of human pharmacokinetic data obviates the need for a complete non-clinical pharmacokinetic profile.

III.5 Toxicology
The oral LD50 of propylthiouracil in male rats is reported as 1.98 g/kg body weight in the Summary of Product Characteristics an authorised propylthiouracil medicinal product. The SPC also reports that in subacute toxicity studies using different methods of administration in rats, toxic effects included reduction of weight gain, hyperplasia of the thyroid gland and hepatomegaly. These effects are consistent with those of a published study, in which repeated intraperitoneal administration of propylthiouracil 0.5-1.5 mmol/kg to rats led to dose-related reductions in body weight, increases in liver weight and reductions in the weight of the spleen. Leucocyte counts markedly decreased in all the treated animals. Histopathological changes were seen as congestion of red pulp of the spleen and vacuolization of the liver.

Oral administration of propylthiouracil 0, 0.1, 1 or 10 mg/kg to groups of 10 male and female Wistar rats led to dose-related reductions in serum thyroxine and tri-iodothyronine and increases in serum thyroid stimulating hormone (TSH) as expected from pharmacological studies. Reduced organ weights, anaemia, impaired blood coagulation, reduced activity of enzymes, hypertrophy/hyperplasia of the thyroid gland and hyperplasia of basophilic and acidophilic cells in the pituitary gland were also noted in this study. The results are consistent with the increased weights of the thyroid gland and pituitary gland, hypertrophy of follicular epithelial cells in the thyroid gland and increase in basophilic cells in the pituitary gland associated with propylthiouracil in a pharmacology study described above.

An intravenous dose of propylthiouracil 10 mg/kg in rabbits led to an immediate fall in serum T3 concentrations, accompanied by a reduction in respiration rate and cutaneous blood flow. Renal blood flow increased simultaneously and arterial blood pressure fell slightly. The mean core temperature of the animals increased by 1.1°C.

As discussed in the section on pharmacology on page 8, propylthiouracil is thought to have immunomodulatory properties. The drug was associated with Coombs’-positive haemolytic anaemia, thrombocytopenia and increased serum antinuclear antibodies in 9/105 cats undergoing treatment for hyperthyroidism.

Genotoxicity
Data concerning the genotoxic potential of propylthiouracil are limited, and the studies were conducted many years ago, many of the studies conducted (all without metabolic activation) appear to be negative. The product will be used as a replacement for other available propylthiouracil products and the genotoxic risk to the patient remains unchanged.
Propylthiouracil 50 mg Tablets

Carcinogenicity
The SmPC for a similar marketed product states that in some short-term studies, rats and rodents made markedly hypothyroid by treatment with high doses of propylthiouracil developed thyroid hyperplasia, adenomas, carcinoma, pituitary adenomas and parathyroid hyperplasia.

Reductions in the levels of thyroxine (T4) and tri-iodothyronine (T3) and increases in thyroid-stimulating hormone (TSH) have been proposed to mediate the proliferation of thyroid follicular cell proliferation and potential thyroid tumour-promoting effects of antithyroid drugs such as propylthiouracil. TSH is known to stimulate thyroid gland function and growth as well as neoplasia. Male Sprague-Dawley rats fed propylthiouracil 30 p.p.m. in the diet for 3-90 days showed a 90 % reduction in serum T4, a 500% increase in thyroid weight and an 830 % increase in TSH levels. Thyroid cell proliferation peaked at 850 % on day 7 but returned to control levels by day 45 of treatment.

Pronounced effects have been seen when propylthiouracil is administered with known carcinogenic substances. Concomitant administration with N-bis(2-hydroxypropyl) nitrosamine promoted the development of thyroid tumours in Wistar rats, although rats given propylthiouracil alone in a previous study showed no thyroid tumours, papillary carcinomas or solid tumours. Serum levels of TSH did not correspond with the tumour-promoting effect of propylthiouracil.

In a later study, propylthiouracil was associated with a significant increase in the growth rate of oestrogen receptor-positive thyroid tumour lines in rats.

Based on data from animal studies, it is possible that propylthiouracil is a human carcinogen although available clinical data have not established a link between propylthiouracil exposure and cancer. Benign and malignant thyroid and parathyroid tumours have been reported following oral exposure in rodents. As a consequence, section 5.3 of the SPC broadly reports these findings using identical wording to that of the similar marketed product.

The mechanism is likely linked to the pharmacological action of the drug, resulting in reductions in T3 and T4 and an increase in TSH. It should be remembered that the animals used in the literature studies do not represent the clinical situation i.e. (healthy animals verses patients with hyperthyroidism) and it is likely that the carcinogenesis observed is associated with the hypothyroid state. As per the product information the dose of propylthiouracil will be closely monitored by measuring thyroid hormone levels. The selection of an appropriate dose will not only ensure that efficacy is achieved and maintained but also that overtreatment and induction of hypothyroidism is avoided.

Reproductive and developmental toxicity
Propylthiouracil crosses the placenta and passes into breast milk in low concentrations. Placental transfer of the drug has been demonstrated in vitro (the isolated perfused human placenta) and in vivo (rats).

Exposure to propylthiouracil during murine embryogenesis has recently been reported to be associated with delayed neural tube closure, cardiac abnormalities and foetal loss. A total of 134 differentially expressed genes were identified following propylthiouracil treatment in this study. Genetic pathways associated with cytoskeleton remodelling and keratin filaments were disrupted. No gross malformations of offspring were seen, but a reduction in the numbers of viable embryos per dam indicated a loss of malformed embryos in comparison with controls. No other reports of teratogenic effects in animals were retrieved from the published literature.
The published literature includes many studies of the effects on the offspring of pregnant animals exposed to propylthiouracil. However, the Applicant points out that the drug was generally used for the deliberate induction and investigation of the effects of hypothyroidism during pregnancy, and little information is available about the effects of its therapeutic use for the correction of hyperthyroidism in pregnant animal models.

The effects of oral propylthiouracil on thyroid function during pregnancy and lactation have been studied in mice. Maternal administration of the drug started on day 15 of pregnancy. On sacrifice of the animals on days 6-18 after birth, hypertrophy of the thyroid glands of the pups and mothers was noted and was attributed to increased pituitary levels of TSH. The appearance of thyroid follicles was consistent with hypothyroidism. Thyroid iodine concentrations were greatly reduced in 6- to 14-day old pups and the mothers and were accompanied by reductions in free triiodothyronine and thyroxine concentrations. These effects could explain the perturbations of the pups’ growth that occurred in the study.

### III.6 Impurities
The active substance is stated to comply with the requirements of its European Pharmacopoeia (Ph. Eur.) monograph. Impurity levels are therefore controlled in accordance with the requirements of the monograph.

### III.7 Environmental Risk Assessment
Since this product will be used as a substitute of other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

### III.8 Discussion on non-clinical aspects
There are no objections to the approval of Propylthiouracil Tablets from a non-clinical point of view.

### IV CLINICAL ASPECTS

#### IV.1 Introduction
No new clinical pharmacology data, efficacy data or safety data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of propylthiouracil.

The applicant’s clinical overview includes 95 references dating from 1975 to 2014 and has been written by an appropriately qualified person and is considered acceptable.

#### IV.2 Pharmacokinetics
Propylthiouracil is well absorbed after oral administration and peak plasma concentrations are attained within 1-2 hours. Around 50 -75% of the administered dose is absorbed. There are wide inter-individual variations in absorption. Food has minor effect on absorption but marked effect on plasma concentration-time curves as compared to fasted state.

Propylthiouracil is concentrated in the thyroid gland (its primary site of action) by an active transport mechanism. Its duration of action is more closely related to its concentration in the thyroid gland than its plasma half-life. Propylthiouracil is about 75% - 80 % protein bound. The volume of distribution of propylthiouracil is about 20-30 litres. Propylthiouracil crosses
Propylthiouracil 50 mg Tablets

the placenta and appears in breast milk at concentrations equivalent to about 10 % of serum concentrations.

Metabolism of propylthiouracil probably occurs in the liver. More than 50 % of a dose is excreted as the glucuronic acid conjugate. Less than 2 % of an administered dose of propylthiouracil is excreted unchanged in the urine.

Propylthiouracil is excreted in the urine as metabolites and unchanged drug. The elimination half-life of propylthiouracil is about 1-3 hours.

Interactions of propylthiouracil with other protein-bound drugs such as aspirin, warfarin and phenylbutazone have been reported.

No age-dependent differences were noted for the extent of absorption, volume of distribution or clearance of the drug, but the rate of absorption was three times higher in the younger subjects than in the elderly subjects.

Since the elimination half-life of propylthiouracil may be increased in patients with renal or hepatic impairment, dosage reductions are recommended

**Overall conclusions on pharmacokinetics**

No new pharmacokinetic data were submitted and none were required for an application of this type. Pharmacokinetic information on propylthiouracil has been gathered from over 50 years of clinical use and this is considered sufficient to support its use in current clinical practice.

**Bioequivalence**

No bioequivalence study has been conducted to support this application. This is appropriate for an application submitted under Article 10a (well-established use).

It is important for well-established use applications to show that the evidence from published literature is applicable to the proposed product. In other words, it is to be demonstrated that this product will perform similar to other propylthiouracil tablets on which the literature is based and any differences that may exist will not be clinically relevant in terms of impact on efficacy or safety.

In this instance the applicant has presented comprehensive biopharmaceutical data to bridge the product to bibliographic data, to show that the formulation of the product, which exhibits rapid dissolution, is not expected to have a significant effect of bioavailability or major patient efficacy or safety concerns.

This applicant justified this approach taking into account that the known pharmacokinetic and pharmacodynamic properties of propylthiouracil and that it is not a narrow therapeutic index drug.

The applicant argues that due to the above factors, any differences in bioavailability of different oral formulations of propylthiouracil will have little clinical significance with respect to efficacy/safety of treatment.
IV.3 Pharmacodynamics
Propylthiouracil acts by interfering with the synthesis of T4 and T3 via inhibition of peroxidase in the thyroid gland. It appears to interfere with peroxidase-mediated incorporation of iodine into tyrosyl residues of the precursor thyroglobulin. It also inhibits the coupling of these iodotyrosyl residues to form iodothyronines. There is some evidence that the coupling reaction is more sensitive than the iodination reaction to the inhibitory effects of propylthiouracil (Goodman and Gilman 2011).

Propylthiouracil also partially inhibits the peripheral deiodination of thyroxine (T4) to the active form tri-iodothyronine (T3), thereby reducing T3 formation in the liver and many other tissues. This secondary mode of action is more important in cases of severe hyperthyroidism than in the treatment of mild disease states.

Repeated therapeutic doses of oral propylthiouracil in hyperthyroid patients led to a gradual reduction in serum thyroid hormone levels over several weeks. However, there are a number of studies in severe hyperthyroidism which show that there is a prompt but modest decrease in T3 levels after administration of propylthiouracil.

Treatment of hyperthyroidism with antithyroid drugs has been associated with reductions in the concentration of thyroid-stimulating immunoglobulins in the circulation. Propylthiouracil induced vasodilation and increased differentiation of vascular smooth muscle cells have been reported.

IV.4 Clinical Efficacy
Propylthiouracil has been used in the management of hyperthyroidism, including Grave’s disease (Basedow’s disease) and autonomic toxic adenoma of the thyroid gland since the 1940s. It has also been used for the preparation of hyperthyroid patients for thyroidectomy or radio-iodine therapy.

The proposed dose of propylthiouracil for the treatment of hyperthyroidism in adults (including the elderly) is 300-600 mg daily in single or divided doses until the patient becomes euthyroid (generally within about 1-2 months). A maintenance dose of 50-150 mg daily may then be used. Treatment usually needs to be continued for 1-2 years.

Children aged over 10 years should receive an initial dose of 150-300 mg daily in single or daily doses. The initial dose in children aged 6-10 years is 50-150 mg daily in single or divided doses. The product is not recommended for use in children younger than six years.

The primary aim of treatment of hyperthyroidism is to achieve remission from the disease whilst avoiding hypothyroidism due to over-treatment. A realistic target for treatment with any antithyroid drug is to achieve a remission rate of about 40-60 % (Weetman 2010). Peak remission rates generally occur 18-24 months after starting treatment.

The therapeutic response to propylthiouracil may be expected to be gradual. Only when pre-formed thyroid hormones are depleted and concentrations of circulating thyroid hormones begin to decline do clinical effects become noticeable. Hyperthyroidism does not usually improve until 3-6 weeks after the initiation of treatment with antithyroid drug.

There are no placebo-controlled studies in literature on the efficacy of propylthiouracil in the treatment of hyperthyroidism, probably because such studies would be considered unethical. However, evidence is available from a number of uncontrolled studies or active comparator studies.
One important indication for the use of propylthiouracil is in patients who experience adverse reactions to other antithyroid drugs. Propylthiouracil may be used to render patients euthyroid prior to thyroidectomy in order to reduce operative morbidity and mortality. However, evidence from a number of studies suggests that antithyroid drugs including propylthiouracil should be discontinued at least one week before initiating radio-iodine therapy in order to reduce the risk of treatment failure. Propylthiouracil has found particular use in the treatment of Graves’ disease during pregnancy as there have been concerns about potential teratogenic effects of other antithyroid drugs, and radioactive iodine therapy is contraindicated during pregnancy.

IV.5 Clinical Safety

No new safety data were submitted and none were required for this bibliographic application. Safety is adequately reviewed in the clinical overview. Propylthiouracil has been in clinical use for the oral treatment of hyperthyroidism since the 1940s.

The adverse events reported with use of propylthiouracil include agranulocytosis, hepatotoxicity, drug induced hypersensitivity, cholestasis, vasculitis, neutropenia, purpuric urticarial popular rash. The drug induced hypersensitivity may include manifestations of polyarthritis, cutaneous vasculitis, leukocytoclastic vasculitis and fever. Propylthiouracil-induced vasculitis can range from mild forms with rash and/or arthralgia to haemorrhage and life-threatening renal or pulmonary symptoms.

Other less frequent adverse reactions to propylthiouracil include arthralgia, paraesthesia, headache, gastrointestinal symptoms including nausea, skin pigmentation and hair loss. Impaired olfactory function has been reported. There have been rare reports of nephritis, interstitial pneumonia and isolated case reports of haemolytic anaemia. Overtreatment may result in hypothyroidism leading to goitre.
IV.6 Risk Management Plan (RMP)
The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Propylthiouracil 50 mg Tablets.

A summary of safety concerns and planned risk minimisation activities, as detailed in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>• Hypersensitivity to propylthiouracil or any of the excipients</td>
</tr>
<tr>
<td>• Severe hepatic reactions</td>
</tr>
<tr>
<td>• Previous severe hypersensitivity reaction including: agranulocytosis, hepatitis, vasculitis and nephritis.</td>
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<tr>
<td>• Thrombocytopenia</td>
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<tr>
<td>• Use in patients with hepatic impairment</td>
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<tr>
<td>• Use in patients with renal impairment</td>
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<tr>
<td>• Use in patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>• Drug-drug interactions</td>
</tr>
<tr>
<td>- Theophylline, digoxin, and heart-blockers</td>
</tr>
<tr>
<td>- Radio-iodine therapy</td>
</tr>
<tr>
<td>• Foetal goitre and hypothyroidism (via in-utero exposure)</td>
</tr>
<tr>
<td>• Overdose</td>
</tr>
<tr>
<td>• Changes in infant thyroid function (via exposure from breast milk)</td>
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<tr>
<td>Missing information</td>
</tr>
<tr>
<td>• None</td>
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</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects
There are no objections to the approval of this application from a clinical point of view.

V USER CONSULTATION
A user consultation with target patient groups on the PIL has been performed and the results provided are acceptable.

VI. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Propylthiouracil 50 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
There are no objections to the authorisation of this product on non-clinical grounds.

EFFICACY
The efficacy of propylthiouracil is well recognised. The applicant has provided a good overall summary of the use of the product to treat hyperthyroidism.
SAFETY
The applicant has provided extensive literature to support the safety of the product and no new or unexpected safety concerns arise from this application.

RISK-BENEFIT ASSESSMENT

It is accepted that propylthiouracil has been used since the 1940s in the treatment of hyperthyroidism and has a well-established favourable benefit-risk profile in this indication.

The applicant has presented an extensive and detailed overview which is appropriate to support an Article 10a application.

The applicant has not undertaken a bioequivalence study and comprehensive biopharmaceutical data to bridge the proposed product to bibliographic data. From the data provided, it is considered that the formulation of the product may not have a significant effect of bioavailability and the biowaiver is granted.

The quality of the product is acceptable and any non-clinical or clinical safety concerns have been fully resolved. The risk benefit is, therefore, considered to be positive.
PRODUCT LITERATURE
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for this medicine agreed within the decentralised procedure; no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
(OUTER CARTON)

1. NAME OF THE MEDICINAL PRODUCT
Propylthiouracil 50 mg Tablets
Propylthiouracil

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains 50 mg of propylthiouracil

3. LIST OF EXCIPIENTS
Also contains lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS
Tablet
28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Not applicable.

8. EXPIRY DATE
EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS
Store in the original package in order to protect from light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Halewood Chemicals Ltd,
The Mill, Horton Road,
Stanwell Moor, Staines,
Middlesex, TW19 6BJ, UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 00042/0205

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

Propylthiouracil 50 mg Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| (OUTER CARTON) |
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| Propylthiouracil 50 mg Tablets |
| Propylthiouracil |
| 2. STATEMENT OF ACTIVE SUBSTANCE(S) |
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| 3. LIST OF EXCIPIENTS |
| Also contains lactose monohydrate. See leaflet for further information |
| 4. PHARMACEUTICAL FORM AND CONTENTS |
| Tablet |
| 56 tablets |
| 5. METHOD AND ROUTE(S) OF ADMINISTRATION |
| Read the package leaflet before use. Oral use. |
| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN |
| Keep out of the sight and reach of children. |
| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |
| Not applicable. |
| 8. EXPIRY DATE |
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### Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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